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THE RELATION OF GASTRIC SECRETION TO HEMATOPOIESIS *

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INTRODUCTION

IN 1833 Beaumont [1] noted, " In febrile diathesis, or predisposition, from whatever cause—obstructed perspiration, undue excitement by stimulating liquors, overloading the stomach with food—fear, anger, or whatever depresses or disturbs the nervous system—the villous coat becomes sometimes red and dry, at other times pale and moist, and loses its smooth and healthy appearance; the secretions become vitiated, greatly diminished, or entirely suppressed; the mucous coat scarcely perceptible; the follicles flat and flaccid, with secretion insufficient to protect the vascular and nervous papillae from irritation. . . . When considerable, and particularly, when there are corresponding symptoms of disease, no gastric juice can be extracted, not even on the application of alimentary stimulus. . . . Whenever this morbid condition of the stomach occurs, with the usual accompanying symptoms of disease, there is generally a corresponding appearance of the tongue."

Such changes, which usually include not only a reduction in volume of gastric juice but an absence in acidity and ferment activity, have been variably referred to as achylia gastrica, anacidity or achlorhydria. Although the literature [2, 3, 4, 5, 6] records innumerable attempts to associate symptoms or disease entities such as cancer of the stomach, anemia, malnutrition, diarrhea, chronic alcoholism and cachexia with these alterations of gastric activity, nevertheless they have been found to exist in a certain percentage of otherwise normal, healthy individuals.[7, 8, 9, 10] Bloomfield and Polland [11] report that 3 to 5 per cent of their clinic patients had achlorhydria and that their symptoms differed in no essential way from those of a similar series of controls with normal gastric contents. Hartfall [12] believes that 14 per cent of the average population of all ages is achlorhydric.

Recently, however, a remarkable series of clinical observations and experiments [13, 14, 15, 16, 17, 18, 19] on the relationship of gastric secretion to anemia

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has reopened the entire question. It is with this aspect of the problem that we are principally concerned.

Achlorhydria and Anemia

Samuel Fenwick [20, 21] in 1877 first clearly emphasized the association of atrophy of the stomach with the fatal anemia the clinical picture of which had been described by Thomas Addison [22] in 1849. Other early studies recorded pathological changes,[23, 24] but Henry and Osler in 1886 were the first to describe the pathology of well documented cases.[25] Thereafter the association of Addisonian anemia with chronic inflammatory changes in the stomach and degeneration of the epithelial and glandular structures gained general acceptance. Fenwick stated that he lacked the means to "collect and subject to chemical tests the gastric fluid during life," and it remained for Cahn and Von Mehring [26] in 1886 to demonstrate definitely the absence of free hydrochloric acid. The occurrence of anacidity has since been widely recognized.[27, 28] In 143 well-documented cases Levine and Ladd [29] found achlorhydria so constant that they concluded it was an invariable feature of the disease. However, instances of true Addisonian anemia with normal gastric acidity have been described, but the number of reported cases only serves to emphasize their extreme rarity.[16, 30, 31] The return of hydrochloric acid following treatment has also been noted.[32, 33, 34]

While the anatomical changes offer a plausible explanation for the lack of secretion, the question still remains whether the gastric pathology precedes or is the cause of the anemia, or whether it is merely part of the picture, perhaps entirely secondary to the other aspects of the disease. The early theory [20, 21, 23, 24, 25] was that the anemia depended "on profound degeneration of the gastric tubules" caused possibly by abuse of alcohol,[25] which reduced the amount of gastric juice to such an extent that the assimilation of food was inadequate to the wants of the body. Much stress was placed on the presence of anacidity long before the onset of anemia.[7, 29, 35, 36, 37] This point of view received support from reports describing the supervention of a similar anemia following gastrectomy in man.[37, 38, 39, 40, 41] However, it is not yet certain that this is invariably true,[42] and there is experimental evidence that gastrectomy in dogs is not followed by anemia.[43] Neusser [44] in 1899 offered the alternative view that the gastrointestinal changes were secondary, and in 1900 Strauss [45] made metabolic studies which revealed no unusual alteration in the utilization of protein or fat in achylia gastrica. Recent studies of Griffiths [46] and Maltby,[47] however, indicate that there is deficient digestion of beef protein by the gastric juice of patients with Addisonian anemia. Hurst,[48] reëmphasized the idea of a primary gastrointestinal defect, arguing that hemolytic and neurotoxic factors might be liberated in the intestine as a result of abnormal bacterial activity on proteins incompletely digested in the stomach. He showed that there was an excessive number of bacteria due to absence of the normal antiseptic action of the gastric juice. Davidson [49]

believes that more critical studies of the gastrointestinal bacteriology of Addisonian anemia both before and after treatment fail to support these ideas. In the light of recent developments Hurst has lately modified his theory.[50]

Other macrocytic anemias closely related to true Addisonian anemia are those of sprue, celiac disease, the anemia of Hill, diarrhea, tropical macrocytic anemia of India, and bothriocephalus anemia. In these diseases there seem to be basic etiologic factors other than parasitism. Achlorhydria is present in many but not all of the cases and the anemia is usually improved by the administration of liver. In certain instances an autolyzed yeast preparation, rich in vitamin B-complex, has been effective.

Older reports noted an anemia with a low color index and small corpuscular diameter [35, 36] as a frequent complication of achlorhydria. Recently there has been described as a specific entity, under the designation idiopathic hypochromic or microcytic anemia,[51, 52, 53, 54, 55, 56] an anemia occurring chiefly in middle-aged women and associated with gastric hypoacidity or anacidity, glossitis, and frequently with menorrhagia. In these patients, administration of iron is followed by rapid improvement with increase of hemoglobin and red cells although the low acidity persists.[56, 57, 58] Bloomfield [59] believes that since achlorhydria is not a constant feature it should not be assigned a primary rôle in pathogenesis. Dameshek [54] writes that clinical features as remissions and relapses, sore tongue, gastrointestinal symptoms and paresthesias definitely relate this disease to Addisonian anemia. It is probably dependent, he believes, upon defective gastric secretion associated with achlorhydria, resulting in an inadequate digestion and assimilation of organic iron which leads to faulty hemoglobin synthesis and improper maturation of red cells in the bone marrow. Consistent with this view is the demonstration by sternal biopsy of a hyperplastic marrow crowded with normoblasts and erythroblasts,[54] the curative effect of large doses of inorganic iron,[58, 60] and the observation by Mettier and Minot [61] that iron is better absorbed when the gastrointestinal medium is acid than when alkaline. While Addisonian anemia responds to liver therapy and not to iron, and microcytic anemia to iron and not liver, occasionally in each disease both are required to obtain a complete remission. Heath reports the occurrence of both Addisonian anemia and idiopathic microcytic anemia in each of three sisters.[62]

In pregnancy there occurs a hypochromic type of anemia similar to idiopathic microcytic anemia and relieved by proper doses of iron. In the last third of pregnancy there develops not infrequently a macrocytic anemia which is invariably associated with achlorhydria and responds usually to liver. Spontaneous recovery follows the termination of the pregnancy. This form is indistinguishable from Addisonian anemia, and it also seems to have a definite etiological relationship to deficiency of the gastric secretion.[63]

Pathogenesis of Addisonian Anemia

A. The Antianemic Factor

Following the provocative experiments of Whipple and his associates on anemia in dogs,[64, 65] Minot and Murphy [66] in 1926 published their important observations on the use of a liver diet in the treatment of Addisonian anemia. The discovery that large amounts of whole liver by mouth induced a rapid and striking improvement,[67] was followed by the demonstration that a protein-free liver extract containing less than 2 per cent of the original material was equally effective.[68] Then came the successful results obtained with kidney,[69] and in 1927 Sturgis and Isaacs [70] announced that whole chopped hog's stomach contained an antianemic factor quite comparable to that in hepatic tissue. Meanwhile Minot, Murphy and Stetson [71] had hypothesized that the response to liver was due to the presence of a specific active principle capable of promoting the growth and maturation of the immature red cells that crowd the bone marrow in the relapse of Addisonian anemia.

Castle and his co-workers sought to correlate the almost constant presence of achylia in the disease with the beneficial effect of liver. The singularly quantitative nature of the response of the patient to therapy suggested the possibility of a deficiency disease. The conception was that gastric digestion failed to elaborate from food the specific antianemic principle present in liver, possibly because lack of acid and pepsin eliminated protein digestion, which is overtly the principal chemical function of the normal stomach. Consistent with this idea was the knowledge that the effective substance in liver extract was probably a nitrogenous base or polypeptide, and so conceivably a derivative of protein.[72, 73]

In a series of experiments,[13, 14, 15, 16] Castle and his associates demonstrated the primary rôle of the gastric disorder in the pathogenesis of the disease. They showed that typical remissions, similar to those produced by liver, could be induced by the daily administration of 200 grams of raw beef muscle previously digested by normal gastric juice, either in the stomach or in vitro. Neither the beef nor the gastric juice was effective alone, nor were the two when fed separately. Moreover hydrochloric acid, pepsin, and rennin were eliminated from consideration by means of similar experiments. In conclusion Castle postulated Addisonian anemia to be a deficiency disease of a new type caused by lack of a substance produced from protein during the course of normal digestion which the defective gastric juice of Addisonian anemia was incapable of elaborating. In the healthy person an *intrinsic factor* is secreted by the gastric mucosa. It is organic in nature, thermolabile, neither acid, pepsin nor rennin but possibly an enzyme. This reacts with an *extrinsic factor* derived from the diet, present in beef muscle and protein in nature, to form a heat stabile antianemic principle which is absorbed and stored in the liver, kidney, and possibly to a lesser extent in all tissues. The remissions following the use of liver and kidney

in Addisonian anemia are explained by assuming the presence of this stored antianemic substance. As a result of atrophic and chronic inflammatory changes, the stomach of the individual with Addisonian anemia does not secrete the intrinsic factor. Isaacs and Goldhamer [74] suggested that the difference between normal gastric juice and that of Addisonian anemia might be quantitative rather than absolute. Repeating Castle's experiment, they fed to a patient with Addisonian anemia beef incubated with 1500 c.c. of gastric juice collected from five patients with the anemia, and obtained a moderate reticulocyte response.

Previously Castle [16] had reported two patients in whom blood pictures of Addisonian anemia occurred in the presence of apparently normal gastric contents, but in which the presence of the intrinsic factor could not be shown. Moreover the presence of the "intrinsic" factor was demonstrated in an individual with achylia gastrica but without anemia, and in three patients with hypochromic anemia who responded to iron but not to liver therapy. A contrary observation was that of Barnett [75] who reported two patients with long-standing anacidity in whose gastric secretions, despite the absence of any anemia, no evidence of intrinsic substance could be found. Barnett [30] also described a patient with otherwise typical Addisonian anemia who possessed gastric juice normal in volume, appearance and acidity and high in content of the intrinsic factor. Castle [76] has recently modified his theory to include such conflicting cases as the latter by assuming that the defect may lie in inadequate absorption of the antianemic substance even if elaborated in adequate amounts. Another link in the chain was added by the work of three groups of investigators,[77, 78, 79] who showed independently that the livers of normal and adequately treated patients with Addisonian anemia contained the antianemic principle, whereas it was absent from the livers of untreated or inadequately treated cases. These observations, then, bear witness to the idea, previously broached, that the factor of storage plays a rôle in hematopoiesis. Furthermore an explanation of the mechanism of the macrocytic anemia which often occurs in cirrhosis of the liver is suggested; and Goldhamer et al.[79, 80] have brought experimental evidence to bear on this point.

Cohn, Minot et al.[68, 72, 73] have analyzed the nature of the potent material in liver. Eliminating from raw minced liver the proteins precipitated at pH 5 and those heat coagulable, and removing all ether and alcohol-soluble extractives, they obtained an alcohol precipitate, extractive G, which contained the active substance. This was thermostabile, neither protein, carbohydrate nor fat in nature, and apparently not a vitamin. Judging from its nitrogen content it seemed to be either a nitrogenous base or a polypeptide. Liver Extract 343 N.N.R. is essentially the fraction G of Cohn.

Potent extracts of liver have proved satisfactory when given by mouth [71, 81] and also when administered parenterally.[82, 83, 84, 85, 86, 87] Orally about nine grams of extract, derived from an equivalent to 300 grams of whole liver, has proved the minimal daily amount which can produce a maxi-

mum reticulocyte response in the relapse phase of the disease.[81, 88] An intense blood crisis may result with a single massive dose of the extract, with striking immediate clinical effects, but the duration is not prolonged.[89] When administered parenterally extracts derived from significantly smaller amounts of liver are effective [90, 91] and the cost of treatment is thereby reduced. In addition, the treatment can be controlled more effectively, and the disturbing variable of intestinal absorption circumvented. Isaacs, Sturgis et al.[92] have recently prepared a product for intravenous administration by treating the extract with acetone after filtering through permutite. An injection of material derived from 125 grams of liver produced an average maximum reticulocytosis higher than that reached after about 40 times as much material taken by mouth in divided daily doses.

Another thread was woven into the story of liver when Reimann [93] found a marked increase in potency of material digested in normal human gastric juice. Walden and Clowes [94] produced a very active preparation by the interaction of liver with small amounts of fresh hog gastric tissue. Fouts and Zerfas corroborated this finding using the product called extralin.[95] Later Helmer, Fouts and Zerfas [96] repeated their experience by incubating subminimal quantities of the extract with normal gastric juice. Finally Herron and McEllroy [97] accomplished the same potentiation of liver without gastric juice by the simple process of allowing the liver to stand at warm temperatures and permitting autolysis to take place. In 13 cases they found that the oral dose of autolyzed liver approached the intramuscular requirements of other preparations. They ventured the hypothesis that this increase in potency was due to hydrolysis of the nucleoproteins of the liver by the autolytic enzymes which are present in every cell as well as the stomach, but which differ from the proteolytic enzymes, pepsin and trypsin, in that the latter only slightly affect nucleoproteins.[98] In a similar series of patients we have been able to verify the fact that autolyzed liver has an enhanced potency but we are not prepared to go as far as McEllroy and Herron in comparing it with parenteral dosage.

The development of the concept of an antianemic factor formed by the interaction of an intrinsic and an extrinsic principle, took an unexpected turn when Morris and his co-workers found that the single injection of normal, concentrated, neutralized gastric juice produced an intense and prolonged reticulocyte response and remission in patients with Addisonian anemia.[17, 18, 19, 99] In two classical cases [100] the single intramuscular injection of five and eight cubic centimeters of material equivalent to 3200 and 5700 c.c., respectively, of native swine gastric juice produced a marked reticulocytosis of 34 and 44 days' duration followed by a rapid increase in hemoglobin and red cells. The active principle was demonstrated in the gastric juice of man, swine and dogs, and found to be heat labile, dialyzable through a collodion sac, presumably exhaustible, and able to withstand chemical treatment known to destroy enzymes.[17, 18, 19] It was tentatively considered to be in the nature of a hormone normally secreted internally by the stomach, and

designated *Addisin* by them. Conner [101] confirmed the findings of Morris by injecting normal concentrated human gastric juice into one patient with Addisonian anemia. Wilkinson,[102] however, reported negative results but he neutralized the human gastric juice previous to vacuum distillation, a procedure which apparently inactivates the hematopoietic substance. One of the authors (S. K.) was able to demonstrate a hemopoietic substance in the concentrated gastric juice of dogs when injected into rabbits. Fouts, Helmer, and Zerfas [103] took up these studies and found that fresh normal human gastric juice concentrated at ice box temperatures by ultrafiltration in about 48 hours was inactive on intramuscular injection in patients with Addisonian anemia. When, however, this inactive material was diluted with water, and then reconcentrated by vacuum distillation at 40° C. it proved very potent. Moreover, while fresh juice was inactive, storage of the secretion on ice for two months, and then concentration by ultrafiltration yielded a material which was entirely effective. Apparently before the gastric juice becomes potent, a chemical reaction must take place, which proceeds rapidly at temperatures around 40° C., slowly at ice box temperatures, and not at all above 60° C.

These reports concerning the effects of injected gastric juice came as disturbing elements into an otherwise perfect picture. The obvious explanation, to reconcile them with Castle's concepts, was that the inspissated gastric juice was merely a concentrate of the intrinsic factor which interacted with the extrinsic factor of muscle protein at the site of injection. When investigation [103] failed to reveal evidence of necrosis or pathological change at the site of injection, it was suggested that the interaction might occur at some more remote point. To this argument there was no direct answer but if it were true, then gastric juice concentrated by ultrafiltration and shown to contain the intrinsic factor should be equally effective, which Fouts, Helmer and Zerfas [103] pointed out was not the case. Finally, Minot [104] noted that fever, chills and malaise accompanied the injection of gastric juice [99, 100, 101] and that the sustained reticulocyte response was suggestive of a toxic effect similar to that occasionally seen following injections of arsenic formerly used in the treatment of pernicious anemia. However, Morris and his associates [100] have been able to eliminate all untoward reactions by means of an acetone extract of gastric fluid, and it had previously been shown by others [102, 103] that the same systemic reactions occurred following injections of gastric juice which failed to stimulate the bone marrow. Fouts, Helmer, and Zerfas [103] have come to the conclusion that gastric juice contains both the intrinsic and extrinsic factors which interact to form a hemopoietic agent during the process of vacuum distillation at 40° C. We are inclined towards this explanation and to suggest that the extrinsic factor present is derived either from the protein of gastric mucin or cellular débris, a point which awaits experimental trial.

There is evidence that the injection of concentrated gastric juice causes an increase in leukocytes as well as erythrocytes.[19] According to Morris [19]

the factor in gastric juice which stimulates reticulocytosis is thermolabile whereas the polymorphonuclear leukocytosis is induced by a thermostabile principle. Using canine gastric juice, injected into rabbits under controlled conditions, one of us (S. K.) has been able to induce a similar leukocyte and reticulocyte response, but a separation of two principles by means of heat could not be accomplished.

Morris and his associates [106] have suggested the possibility that erythremia might be due to an excess of the hematopoietic principle in gastric juice which they believe is a hormone and have called Addisin. A patient with erythremia was subjected to gastric lavage over a period of six months, during which time the number of red blood cells decreased from 10,000,000 per cu. mm. to 5,300,000 and subsequently returned to the former level when lavage was discontinued. This was attributed to the mechanical withdrawal of Addisin. The implications of these ideas stimulate the imagination, and it is hoped that they will likewise stimulate further research to test their validity.

B. Vitamin B

The literature records only a few investigations of the influence on gastric secretion of a dietary régime deficient in the vitamin B-complex. Moreover interpretation of these is unsatisfactory because of the complex nature of vitamin B and because the unequivocal production of either vitamin B_1 or B_2 (G) deficiency has not in most instances been established.[107] Danysz and Koskowski [108] and Farnum [109] reported a marked decrease in both volume and acidity of secretion, the former in pigeons fed on a ration of polished rice and the latter in Pavlov pouch dogs who received a diet autoclaved in alkaline medium to destroy the antineuritic factor. Cowgill and Gilman [110] observed the development of gastric achlorhydria in dogs that were given rations lacking vitamin B-complex. Complete anacidity was produced by Webster and Armour under absolute avitaminosis in dogs without the exhibition of anorexia or inanition.[111, 112] Gastric secretion was restored by autoclaved and by powdered yeast, and lost when these were withdrawn. The authors believed that the vitamins contained in yeast were absolutely essential to the normal secretory activity of the gastric mucosa. Recently Miller and Rhoades [113] produced in dogs a syndrome similar to clinical sprue, with feedings deficient in vitamin B_2 by a modification of the Goldberger black tongue producing diet. There were glossitis, anorexia, vomiting, striking diarrhea and loss of weight. The blood changes were marked, and microscopic studies of the bone marrow revealed pictures virtually indistinguishable from those of sprue. No studies on gastric secretion were reported.

Some evidence has been advanced that deficiency in vitamin B-complex, and especially of the B_2 factor, may be responsible for the atrophic glossitis which is frequently associated with achlorhydria and anemia. Very significant from a clinical viewpoint is the obvious parallelism between pellagra,

sprue, and Addisonian anemia in their common glossitic and gastrointestinal manifestations,[114] and the frequent occurrence of anacidity in pellagra. That glossitis may be present with normal gastric secretion, however, is shown in certain cases of sprue and idiopathic microcytic anemia. Lewis [115] believes the smooth tongue in all probability represents a deficiency manifestation. In a patient with sprue he observed that absence of the intrinsic factor occurred in the presence of a normal tongue. With a diet deficient in vitamin B-complex Hutter and Middleton [116] produced smooth tongue in rats. A high vitamin B-complex ration given by them to three patients with Addisonian anemia and glossitis resulted in the clearing up of the glossitis in only one, without affecting the blood picture. In the other two the glossitis improved when a low vitamin B-complex diet and liver were subsequently given. The question was raised as to whether smooth tongue may not be a conditioned deficiency in which the absorption and assimilation of the lower vitamin intake may be rendered more adequate by liver extract. That the parenteral administration of liver extract alone clears up glossitis is significant when one recalls that liver and liver extract are themselves rich in vitamins B_1 and B_2.[117, 118, 119, 120]

In the meantime Wills [121] in India reported cases of tropical macrocytic anemia, similar to Addison's anemia though with or without achlorhydria, cured by an autolyzed yeast product, marmite, rich in vitamin B_2. This substance was found to equal liver extract in its efficacy.[122] It was subsequently used successfully in treating celiac disease with a macrocytic anemia and free gastric acidity,[122] in cases of sprue [123] and apparently in certain cases of true Addisonian anemia.[124, 125, 126] Connery and Goldwater [127] obtained a typical reticulocyte response in two of four patients with classical Addisonian anemia by the oral administration of vitamin B-complex alone. Russell [128] gave small doses of brewer's yeast to four cases of true Addisonian anemia and obtained slight increases in the number of reticulocytes. The subsequent administration of liver extract parenterally was followed by a greater reticulocytosis and characteristic remission. Lassen and Lassen [129] tested various yeast preparations on eight patients with Addisonian anemia and concluded that yeast was without antianemic effect or possibly it contained minimal amounts of the antianemic factor. Cohn et al.[68, 72] reported essentially negative results in treatment by the feeding of 120 grams of yeast cake daily and with various concentrates of vitamin B. Strauss and Castle [119] and Davidson [130] found autolyzed yeast alone inert.

Strauss and Castle considered the possibility that marmite might contain the extrinsic factor which they believed interacted with the intrinsic factor present in normal human gastric juice to form the hematopoietic substance.[119] On using an autolyzed yeast preparation similar to marmite called Vegex incubated with normal gastric juice, or Vegex after autoclaving for five hours to destroy vitamin B_1 or an 80 per cent alcoholic extract of the preparation, it was found that in doses equivalent to 12 grams of marmite, each of these mixtures produced typical reticulocyte crises and remissions in Addi-

sonian anemia. They concluded that the extrinsic factor was a substance closely related to vitamin B_2, if not vitamin B_2 itself. The suggestion was made that the cases of sprue, tropical macrocytic anemia and celiac disease which had responded to the administration of yeast, had been due to lack of the extrinsic factor, and that the intrinsic factor has been present in the gastric juice. Consistent with this hypothesis was the observation that the protein extract of washed beef muscle originally used by Castle as a source of the extrinsic factor, was rich in vitamin B_2 [87] as are also commercial liver extracts and stomach preparations.[117, 118, 119, 120] Since Liver Extract 343 is rich in vitamin B_2,[120] the potentiation of this extract with hog stomach by Walden and Clowes was readily explained.

Wills,[132] however, believed that the use by Strauss and Castle of 80 per cent alcohol would inactivate or destroy vitamin B_2 as has been stated by Chick and Copping.[133] She found that dried brewer's yeast and a watery yeast extract, both rich in vitamin B_2, and egg white containing doses of the principle seven times that of marmite, all failed to produce results in patients with tropical macrocytic anemia who then responded excellently to marmite. While dried brewer's yeast was without effect, marmite, which is an autolyzed extract made from brewer's yeast, was specifically curative. The responsible factor was heat stabile and alcohol soluble. She concluded that autolysis broke down some of the protein into simpler products and that the marmite probably owed its properties to one of these. Subsequently, Wills and Naish [134] treated a classical case of Addisonian anemia with vitamin B_2 from egg white. Both egg white alone, and egg white incubated with normal gastric juice given daily were without effect, following which the patient received by mouth the equivalent of one pound of liver daily with excellent result. They believed that the extrinsic factor was not vitamin B_2, but some other substance present in both animal protein and marmite. To this point of view Castle has recently subscribed.[135]

Comment

The development of thought on the relationship of gastric secretion and hematopoiesis has taken place with amazing rapidity. Not only have important advances in the understanding and treatment of disease been made but new and equally significant contributions to fundamental physiology as well have been added. A brief summary of what has been learned may be stated as follows:

The dependence of hematopoiesis upon normal gastric function has been established. While gross disturbances in the chemical composition of gastric secretion may play a rôle in the pathogenesis of certain microcytic hypochromic anemias, the development of Addisonian and related macrocytic anemias is conditioned not upon these gross disturbances but upon one or more of the following:

(*a*) Diminution or absence of a substance in gastric secretion, an intrinsic factor.

(*b*) Reduced oral intake of a substance derived from certain protein foods, the extrinsic factor.

(*c*) Deficient absorption of an antianemic substance formed by the interaction in vivo and vitro of the intrinsic and extrinsic factors.

(*d*) Impaired storage of the antianemic substance principally in the liver.

The intrinsic factor has been shown to be organic in nature, thermolabile, neither acid, pepsin nor rennin but probably an enzyme. The extrinsic factor is found in certain but not all meats and autolyzed yeast. Its presence in casein and gluten could not be demonstrated. Its identity as vitamin B_2 has been disproved, and certain assays of nucleoproteins and nucleic acid have failed to reveal it. The antianemic principle is thermostabile, and has been identified as a nitrogenous base or polypeptide. It is found in the livers of normal individuals or patients with Addisonian anemia adequately treated, and absent from the livers of patients in relapse or inadequately treated. It has been found in animal livers and kidneys and desiccated hog's stomach. The injection of normal gastric juice concentrated by vacuum distillation results in a prolonged reticulocytosis and remission of Addisonian anemia. When substances containing the antianemic principle are subjected to (*a*) interaction with gastric juice, (*b*) interaction with gastric tissue, or (*c*) autolysis, an unexplained increase in antianemic potency is effected.

Although the contributions that have been made fit into an orderly mosaic, the outline and dimensions of which have been fairly well defined, there are still many large gaps in the pattern. One of the most important of these is the determination of the exact nature of Castle's intrinsic factor. If it is an enzyme its properties, actions, source, and relation to the autolytic enzymes in tissue cells await elucidation. The explanation of the conflicting results when nucleoproteins were used as the source of the extrinsic factor may throw some light on the nature of this factor and its relation to nucleoproteins. The mechanism of the action of injected concentrated gastric juice is still obscure and attempts to reconcile it with Castle's ideas are not altogether convincing.

A further study of gastric function and of the dietary of herbivora, especially in regard to the extrinsic factor, seems warranted. The consistent failure to produce a macrocytic anemia in animals by gastrectomy suggests that in these the duodenum or some other portion of the gastrointestinal tract may be concerned in the elaboration of the intrinsic factor. Finally there is a vital need for a simpler and more easily controllable method for assaying the antianemic principle. The awakening of widespread interest in the recognition and treatment of pernicious anemia has resulted in a sharp decline in the number of patients that are referred to those who are studying the disease, and progress seems to stand in its own way. But this is not a new problem in medical research.

REFERENCES

1. BEAUMONT, W.: Experiments and observations on the gastric juice and the physiology of digestion, 1833, F. P. Allen, Plattsburgh, New York.

2. Faber, K., and Lange, G.: Die Pathogenese und Aetiologie der chronischen Achylia gastrica, Ztschr. f. klin. Med., 1908, lxvi, 53–89.
3. Riegel, F.: Die Erkrankungen des Magens, 1908, vol. 2, Alfred Hölder, Vienna and Leipzig.
4. Einhorn, M.: On achylia gastrica, New York Med. Rec., 1892, xli, 650–654.
5. Oppler, B.: Über die Abhängigkeit gewisser chronischer Diarrhöen von mangelnder Sekretion des Magensaftes, Deutsch. med. Wchnschr., 1896, xxii, 511–514.
6. Tabora, D.: Die Darmerscheinungen bei Achylia gastrica, München. med. Wchnschr., 1904, li, 865–868.
7. Wilkinson, J. F., and Oliver, T. H.: Some clinical conditions associated with achlorhydria, Lancet, 1931, i, 66–71.
8. Keefer, C. S., and Bloomfield, A. L.: The significance of gastric anacidity, Bull. Johns Hopkins Hosp., 1926, xxxix, 304–329.
9. Eggleston, E. L.: Pathological conditions secondary to achlorhydria, Jr. Am. Med. Assoc., 1931, xcvii, 1216–1221.
10. Polland, W. S., and Bloomfield, A. L.: Unexplained gastric anacidity, Arch. Int. Med., 1931, xlviii, 412–417.
11. Bloomfield, A. L., and Polland, W. S.: Gastric anacidity, 1933, Macmillan Co., New York.
12. Hartfall, S. J.: Some observations on achlorhydria and anemia, Brit. Med. Jr., 1934, i, 136–141.
13. Castle, W. B.: Observations on the etiological relationship of achylia gastrica to pernicious anemia. I. The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle, Am. Jr. Med. Sci., 1929, clxxviii, 748–764.
14. Castle, W. B., and Townsend, W. C.: Observations on the etiological relationship of achylia gastrica to pernicious anemia. II. The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal gastric juice, Am. Jr. Med. Sci., 1929, clxxviii, 764–777.
15. Castle, W. B., Townsend, W. C., and Heath, C. W.: Observations on the etiological relationship of achylia gastrica to pernicious anemia. III. The nature of the reactions between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to the effect of liver feeding, Am. Jr. Med. Sci., 1930, clxxx, 305–335.
16. Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the etiological relationship of achylia gastrica to pernicious anemia. IV. A biological assay of the gastric secretion of patients with pernicious anemia, Am. Jr. Med. Sci., 1931, clxxxii, 741–764.
17. Morris, R. S., and Schiff, L.: Reticulocyte response in pernicious anemia following intramuscular injection of gastric juice, Jr. Med., 1932, xiii, 27.
18. Morris, R. S., Schiff, L., Berger, G., and Sherman, J. E.: A specific hematopoietic hormone in normal gastric juice, Jr. Am. Med. Assoc., 1932, xcviii, 1080–1081.
19. Morris, R. S., Schiff, L., Berger, G., and Sherman, J. E.: The hematopoietic response in pernicious anemia following the intramuscular injection of gastric juice, Am. Jr. Med. Sci., 1932, clxxxiv, 778–782.
20. Fenwick, S.: On atrophy of the stomach in relation to pernicious anemia, Lancet, 1877, ii, 1–4, 39–41, 77–78.
21. Fenwick, S.: On atrophy of the stomach, 1880, J. and A. Churchill, London.
22. Addison, T.: A collection of the published writings of the late Thomas Addison, 1868, New Sydenham Society, London.
23. Quinke, H.: Weiteren Beobachtungen über perniciöse Anämie, Deutsch. Arch. f. klin. Med., 1877, xx, 1–31.
24. Kinnicutt, F. P.: Atrophy of the gastric tubules—its relation to pernicious anemia, Am. Jr. Med. Sci., 1887, xciv, 419–443.

25. HENRY, F. P., and OSLER, W.: Atrophy of the stomach with the clinical features of progressive pernicious anemia, Am. Jr. Med. Sci., 1886, xci, 498–511.
26. CAHN, A., and VON MEHRING, J.: Die Säuren des gesunden und kranken Magens, Deutsch. Arch. f. klin. Med., 1886, xxxix, 233–253.
27. GRAWITZ, E.: Klinische Pathologie des Blutes, 1896, O. Enslin, Berlin.
28. FABER, K., and BLOCH, C. E.: Über die pathologischen Veränderung im Digestiontractus bei der perniciösen Anämie, Ztschr. f. klin. Med., 1900, xl, 98–141.
29. LEVINE, S. A., and LADD, W. S.: Pernicious anemia: a clinical study of 150 consecutive cases with special reference to gastric anacidity, Bull. Johns Hopkins Hosp., 1921, xxxii, 254–266.
30. BARNETT, C. W.: The significance of gastric secretions in pernicious anemia, Am. Jr. Med. Sci., 1931, clxxxii, 170–177.
31. HARVEY, E. A., and MURPHY, W. P.: Pernicious anemia without achlorhydria, ANN. INT. MED., 1933, vi, 1393–1406.
32. SHAW, M. E.: A case of apparent recovery from Addison's anemia and the associated achlorhydria, Guy's Hosp. Rep., 1926, lxxvi, 294–302.
33. HURST, A. F.: Restoration of gastric secretion in Addison's anemia by treatment of the gastritis, Guy's Hosp. Rep., 1930, lxxx, 407–410.
34. MCPEAK, E. M., and NEIGHBORS, D.: Minot-Murphy diet in pernicious anemia: report of five cases, South. Med. Jr., 1927, xx, 926–931.
35. FABER, K.: Anämische Zustande bei der chronischen Achylia gastrica, Berlin. klin. Wchnschr., 1913, 1, 958–962.
36. FABER, K., and GRAN, H. C.: Relation between gastric achylia and simple and pernicious anemia, Arch. Int. Med., 1924, xxxiv, 658–668.
37. HURST, A. F.: Achlorhydria: its relation to pernicious anemia and other diseases, Lancet, 1923, i, 111–115.
38. MOYNIHAN, B. G. A.: A case of complete gastrectomy, Lancet, 1911, ii, 430–431.
39. HARTMAN, H. R.: Blood changes in a gastrectomized patient simulating those of pernicious anemia, Am. Jr. Med. Sci., 1921, clxii, 201–206.
40. UNGLEY, C. C.: The stomach and pernicious anemia, Newcastle Med. Jr., 1929, x, 14–39.
41. DENNIG, H.: Perniziöse Anämie nach Magenresektion, München. med. Wchnschr., 1929, lxxvi, 633.
42. WALTERS, W.: Total gastrectomy for carcinoma; physiologic and chemical studies during period of two years following operation, Jr. Am. Med. Assoc., 1933, c, 804–806.
43. IVY, A. C., MORGAN, J. E., and FARRELL, J. I.: The effects of total gastrectomy; experimental achylia gastrica in dogs with occurrence of spontaneous anemia, Surg., Gynec. and Obst., 1931, xliii, 611–620.
44. NEUSSER, H.: Zur Klinik der perniciösen Anämie, Wien. klin. Wchnschr., 1899, xii, 388–395.
45. STRAUSS, H.: Untersuchungen über die Resorption und den Stoffwechsel bei "Apepsia gastrica" mit besonderer Berücksichtigung der perniciösen Anämie, Ztschr. f. klin. Med., 1900, xli, 280–320.
46. GRIFFITHS, W. J.: The action of gastric juice on beef muscle-globulin, with reference to anemia, Biochem. Jr., 1934, xxviii, 671–675.
47. MALTBY, E. J.: The digestion of beef proteins in the human stomach, Jr. Clin. Invest., 1934, xiii, 193–207.
48. HURST, A. F.: Achlorhydria and achylia gastrica and their connection with Addison's anemia—subacute combined degeneration syndrome and simple (non-Addisonian) achlorhydric anemia, Quart. Jr. Med., 1932, i, 157–177.
49. DAVIDSON, S.: The etiology of pernicious anemia. A review of the factors concerned in its production, Edinburgh Med. Jr., 1928, xxxv, 322–343.
50. HURST, A. F.: The unity of gastric disorders, Alvarez lecture, Trans. Am. Gastro-Entero. Assoc., 1933, 70–85.

51. Watkins, C. H.: Classification of chronic idiopathic secondary anemia with special reference to morphology of blood, Jr. Am. Med. Assoc., 1929, xciii, 1365–1367.
52. Witts, L. J.: Simple achlorhydric anemia, Guy's Hosp. Rep., 1930, lxxx, 253–296.
53. Waugh, T. R.: Idiopathic hypochromemia, Am. Jr. Med. Sci., 1931, clxxxii, 554–565.
54. Dameshek, W.: Primary hypochromic anemia (erythro-normoblastic anemia); new type of idiopathic anemia, Am. Jr. Med. Sci., 1931, clxxxii, 520–553.
55. Vanderhoof, D., and Davis, D.: Anemia of the microcytic type in middle-aged women, Am. Jr. Med. Sci., 1932, clxxxiv, 29–33.
56. Wintrobe, H. M., and Beebe, R. T.: Idiopathic hypochromic anemia, Medicine, 1933, xii, 187–243.
57. Meulengracht, E.: Simple achylic anemia, Acta. med. Scandinav., 1932, lxxviii, 387–426.
58. Witts, L. J., Davies, D. T., and Mackay, H. M. M.: Discussion on the therapeutic uses of iron, Proc. Roy. Soc. Med. (Sect. Therap. and Pharm.), 1931, xxiv, 7–24.
59. Bloomfield, A. L.: The relations between primary hypochromic anemia and chlorosis, Arch. Int. Med., 1932, l, 328–337.
60. Schulten, H.: The treatment of hypochromic anemia with large doses of iron, München. med. Wchnschr., 1930, lxxvii, 355–356.
61. Mettier, S. R., and Minot, G. R.: Effect of iron on blood formation as influenced by changing acidity of gastro-duodenal contents in certain cases of anemia, Am. Jr. Med. Sci., 1931, clxxxi, 25–36.
62. Heath, C. W.: The interrelation of pernicious anemia and idiopathic hypochromic anemia. Study of family in which both conditions occurred singly and combined, Am. Jr. Med. Sci., 1933, clxxxv, 365–381.
63. Strauss, M. B., and Castle, W. B.: Studies of anemia in pregnancy; etiologic relationship of gastric secretory defects and dietary deficiency to hypochromic and macrocytic (pernicious) anemias of pregnancy and treatment of these conditions, Am. Jr. Med. Sci., 1933, clxxxv, 539–551.
64. Whipple, G. H., and Robscheit-Robbins, F. S.: Blood regeneration in severe anemia. I. Standard basal ration bread and experimental methods, Am. Jr. Physiol., 1925, lxxii, 395–407.
65. Robscheit-Robbins, F. S., and Whipple, G. H.: Blood regeneration in severe anemia. II. Favorable influence of liver, heart and skeletal muscle in diet, Am. Jr. Physiol., 1925, lxxii, 408–418.
66. Minot, G. R., and Murphy, W. P.: Treatment of pernicious anemia by a special diet, Jr. Am. Med. Assoc., 1926, lxxxvii, 470–476.
67. Murphy, W. P., and Minot, G. R.: A special diet for patients with pernicious anemia, Boston Med. and Surg. Jr., 1926, cxcv, 410–411.
68. Cohn, E. J., Minot, G. R., Fulton, J. F., Ulrichs, H. F., Sargent, F. C., Weare, J. H., and Murphy, W. P.: Nature of the material in liver effective in pernicious anemia, Proc. Am. Soc. Biol. Chem., Jr. Biol. Chem., 1927, lxxiv, p. lxix.
69. McCann, W. S.: Effect of kidney on blood regeneration in pernicious anemia, Proc. Soc. Exper. Biol. and Med., 1928, xxv, 255–258.
70. Sturgis, C. C., and Isaacs, R.: Desiccated stomach in the treatment of pernicious anemia, Jr. Am. Med. Assoc., 1929, xciii, 747–749.
71. Minot, G. R., Murphy, W. P., and Stetson, R. P.: Response of reticulocytes to liver therapy; particularly in pernicious anemia, Am. Jr. Med. Sci., 1928, clxxv, 581–599.
72. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: Nature of the material in liver effective in pernicious anemia, Jr. Biol. Chem., 1928, lxxvii, 325–358.
73. Cohn, E. J., McMeekin, T. L., and Minot, G. R.: The nature of the material effective in pernicious anemia, Proc. Am. Soc. Biol. Chem., Jr. Biol. Chem., 1930, lxxxvii, p. xlix–lii.

74. Isaacs, R., and Goldhamer, S. M.: Rôle of decreased amount of gastric secretion in production of pernicious anemia, Proc. Soc. Exper. Biol. and Med., 1934, xxxi, 706–707.

75. Barnett, C. W.: The significance of the gastric secretion in pernicious anemia, Am. Jr. Med. Sci., 1932, clxxxiv, 24–28.

76. Castle, W. B., Heath, C. W., Strauss, M. B., and Townsend, W. C.: The relationship of disorders of the digestive tract to anemia, Jr. Am. Med. Assoc., 1931, xcvii, 904–907.

77. Richter, O., Ivy, A. C., and Kim, M. S.: Action of human "pernicious anemia liver extract," Proc. Soc. Exper. Biol. and Med., 1932, xxix, 1093–1098.

78. Wilkinson, J. F., and Klein, L.: The hemopoietic activity of normal and abnormal human liver with especial reference to pernicious anemia, Quart. Jr. Med., 1934, iii, 341–359.

79. Goldhamer, S. M., Isaacs, R., and Sturgis, C. C.: The rôle of the liver in hematopoiesis, Am. Jr. Med. Sci., 1934, clxxxviii, 193–199.

80. Goldhamer, S. M.: Liver extract therapy in cirrhosis of liver; relation of liver dysfunction to nonstorage of "anti-anemic" substance in producing blood picture resembling pernicious anemia in patient secreting free hydrochloric acid, Arch. Int. Med., 1934, liii, 54–57.

81. Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A.: Treatment of pernicious anemia with liver extract. Effects upon the production of immature and mature red blood cells, Am. Jr. Med. Sci., 1928, clxxv, 599–622.

82. Cohn, E. J., McKeekin, T. L., and Minot, G. R.: Nature of the material effective in pernicious anemia, Am. Jr. Physiol., 1929, xc, 316–317.

83. Gäusslen, M.: Ein hockwirksamer, injizierbar Leberextract, Klin. Wchnschr., 1930, ix, 2099–2106.

84. Schottmüller, H.: Weitere Erfahrungen über die Lebertherapie bei Anaemia perniciosa, München. med. Wchnschr., 1931, lxxviii, 432.

85. Castle, W. B., and Taylor, F. H. L.: Intravenous use of extract of liver. Maximal responses of reticulocytes from single injection derived from 100 grams of liver; preliminary communication, Jr. Am. Med. Assoc., 1931, xcvi, 1198–1201.

86. Strauss, M. B., Castle, W. B., and Taylor, F. H. L.: Intramuscular use of liver extract; maximal responses of reticulocytes from daily intramuscular injection of extract derived from 10 grams of liver; preliminary communication, Jr. Am. Med. Assoc., 1931, xcvii, 313–314.

87. Wilkinson, J. F.: Injections of highly purified liver preparations in pernicious anemia, Lancet, 1931, ii, 791–792.

88. Zerfas, L. G.: Liver extract for pernicious anemia; blood changes during first month; report of 101 cases, Int. Med., 1931, xlvii, 135–143.

89. Riddle, M. C., and Sturgis, C. C.: The effect of single massive doses of liver extract on patients with pernicious anemia, Am. Jr. Med. Sci., 1930, clxxx, 1–11.

90. Murphy, W. P.: Parenteral use of liver extract in pernicious anemia, Jr. Am. Med. Assoc., 1932, xcviii, 1051–1060.

91. Connery, J. E., and Goldwater, L. J.: Parenteral use of liver extract in the treatment of pernicious anemia, Jr. Am. Med. Assoc., 1932, xcviii, 1060–1067.

92. Isaacs, R., Sturgis, C. C., Goldhamer, S. M., and Bethell, F. H.: The use of liver extract intravenously in the treatment of pernicious anemia, Jr. Am. Med. Assoc., 1933, c, 629–633.

93. Reimann, F.: Versuche zur Potenzierung der Wirkung oral verabreichter Leber. Kurze wissenschaftliche Mitteilung, Med. Klin., 1931, xxvii, 880–881.

94. Walden, G. B., and Clowes, G. H. A.: Pernicious anemia: method whereby therapeutic efficacy of liver and liver fractions may be substantially increased, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 873–875.

95. Fouts, P. J., and Zerfas, L. G.: Liver-gastric tissue preparations in the treatment of pernicious anemia, Jr. Am. Med. Assoc., 1933, ci, 188–192.
96. Helmer, O. M., Fouts, P. J., and Zerfas, L. G.: Increased potency of liver extract by incubation with human gastric juice, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 775–778.
97. Herron, W. F., and McEllroy, W. S.: The use of autolyzed liver in the treatment of pernicious anemia; preliminary clinical report, Jr. Am. Med. Assoc., 1933, c, 1084–1086.
98. Herron, W. F., and McEllroy, W. S.: Use of autolyzed liver in anemia and other conditions, Penn. Med. Jr., 1934, xxxvii, 406–408.
99. Morris, R. S., Schiff, L., Foulger, J. H., Rich, M. L., and Sherman, J. E.: Observations on hematopoietic hormone (addisin) in pernicious anemia, Brit. Med. Jr., 1932, ii, 1050–1051.
100. Morris, R. S., Schiff, L., Foulger, J. H., Rich, M. L., and Sherman, J. E.: The treatment of pernicious anemia; effect of single injection of concentrated gastric juice (addisin), Jr. Am. Med. Assoc., 1933, c, 171–173.
101. Conner, H. M.: Increase of reticulated erythrocytes in pernicious anemia following intramuscular injection of gastric juice, Proc. Staff Meet., Mayo Clinic, 1932, vii, 213–216.
102. Wilkinson, J. F.: Hematopoietic hormone in pernicious anemia, Brit. Med. Jr., 1932, ii, 1163.
103. Fouts, P. J., Helmer, O. M., and Zerfas, L. G.: Formation of a hematopoietic substance in concentrated gastric juice, Am. Jr. Med. Sci., 1934, clxxxvii, 36–49.
104. Minot, G. R.: The interpretation of reticulocyte responses in pernicious anemia, Trans. Assoc. Am. Physicians, 1934. (In print.)
105. Helmer, O. M., Fouts, P. J., and Zerfas, L. G.: The relationship of the intrinsic factor to a hematopoietic material in concentrated human gastric juice, Am. Jr. Med. Sci., 1934, clxxxviii, 184–193.
106. Morris, R. S., Schiff, L., Foulger, J. H., and Rich, M. L.: Further studies on addisin in diseases of the blood, Trans. Assoc. Am. Physicians, 1933, xlviii, 298–304.
107. Kruse, H. D., and McCollum, E. V.: Review of recent studies on the antineuritic vitamin; its chemical and physiologic properties, and the effects of its deprivation on the animal body, Jr. Am. Med. Assoc., 1932, xcviii, 2201–2208.
108. Danysz, M., and Koskowski, W.: Étude de quelques fonctions digestives chez les pigeons normaux nourris au riz poli et en inanition, Compt. rend. Acad. d. sc., 1922, clxxv, 54–56.
109. Farnum, M. B.: Gastric secretion in experimental beri-beri in dog, Arch. Int. Med., 1926, xxxvii, 212–216.
110. Cowgill, G. R., and Gilman, A.: Physiology of vitamins. The effect of lack of the vitamin B complex on the secretion of gastric juice in dogs with gastric pouches, Arch. Int. Med., 1934, liii, 58–70.
111. Webster, D. R., and Armour, J. C.: Effect of vitamin B deficiency on gastric secretion, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 1297–1300.
112. Webster, D. R., and Armour, J. C.: Vitamin B complex and gastric secretion, Proc. Soc. Exper. Biol. and Med., 1934, xxxi, 463–464.
113. Miller, D. K., and Rhoades, C. P.: Production in dogs of a syndrome similar to sprue by diets deficient in vitamin B_2, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 540–541.
114. Musser, J. H.: Internal medicine, 1932, Lea and Febiger, Philadelphia.
115. Lewis, G. E.: The smooth tongue—a study in deficiency disease, Practitioner, 1930, cxxv, 749–755.
116. Hutter, A. M., and Middleton, W. S.: Vitamin B deficiency and the atrophic tongue, Jr. Am. Med. Assoc., 1933, ci, 1305–1308.
117. Guha, B. C.: The vitamin B_2 potency of commercial liver extract, Lancet, 1931, i, 864–865.

118. GILROY, E.: Vitamin B content of commercial liver extracts and stomach preparations, Lancet, 1931, ii, 1093–1098.
119. WEST, R.; Communication to STRAUSS, M. B., and CASTLE, W. B.: Nature of extrinsic factor of deficiency state in pernicious anemia and in related macrocytic anemias; activation of yeast derivatives with normal gastric juice, N. Eng. Jr. Med., 1932, ccvii, 55–59.
120. COWGILL, G. R.: Liver Extract 343 N. N. R. is rich in vitamin B_2. (Personal communication.)
121. WILLS, L.: Treatment of "pernicious anemia of pregnancy" and "tropical anemia," with special reference to yeast extract as curative agent, Brit. Med. Jr., 1931, i, 1059–1064.
122. VAUGHAN, J. M., and HUNTER, D.: The treatment by marmite of megalocytic hyperchromic anemia occurring in idiopathic steatorrhea (celiac disease), Lancet, 1932, i, 829–834.
123. CASTLE, W. B., and RHOADES, C. P.: Etiology and treatment of sprue in Porto Rico, Lancet, 1932, i, 1198–1199.
124. GOODAL, A.: The treatment of pernicious anemia by marmite, Lancet, 1932, ii, 781–782.
125. UNGLEY, C. C.: Marmite in pernicious anemia, Lancet, 1932, ii, 867.
126. DAVIDSON, S.: Marmite in pernicious anemia, Lancet, 1932, ii, 919–920.
127. CONNERY, J. E., and GOLDWATER, L. J.: Pernicious anemia, a conditioned deficiency; observations on effect of administration of substance rich in vitamin B complex, N. England Jr. Med., 1933, ccix, 446–450.
128. RUSSELL, H. K.: Hematological response of Addisonian pernicious anemia to brewer's yeast, ANN. INT. MED., 1934, vii, 1398–1402.
129. LASSEN, H. C. A., and LASSEN, H. K.: Yeast or vitamin B_2 as "extrinsic factor" in treatment of pernicious anemia, Am. Jr. Med. Sci., 1934, clxxxviii, 461–472.
130. DAVIDSON, S.: Vitamin B in anemia, Lancet, 1931, ii, 1395–1398.
131. BLOCK, R. J., COWGILL, G. R., and KLOTZ, B. H.: The antineuritic vitamin; method of assay, concentration of vitamin with silver under various conditions, and its solubility in certain organic solvents, Jr. Biol. Chem., 1932, xciv, 765–782.
132. WILLS, L.: The nature of the hematopoietic factor in marmite, Lancet, 1933, i, 1283–1286.
133. CHICK, H., and COPPING, A. M.: Heat stability of (anti-dermatitis, "anti-pellagra") water soluble vitamin B_2, Biochem. Jr., 1930, xxiv, 932–938.
134. WILLS, L., and NAISH, A.: A case of pernicious anemia treated with vitamin B_2 from egg-white, Lancet, 1933, i, 1286.
135. Editor's footnote to article by LASSEN, H. C. A., and LASSEN, H. K.: Yeast or vitamin B_2 as "extrinsic factor" in treatment of pernicious anemia, Am. Jr. Med. Sci., 1934, clxxxviii, 461–472.

TREATMENT OF LOBAR PNEUMONIA BY ARTIFICIAL PNEUMOTHORAX *

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Lobar pneumonia may be considered to be an infectious (usually pneumococcic) lobar atelectasis of the lung. The work of Coryllos and Birnbaum [1] and others has strengthened this conception of the disease. The

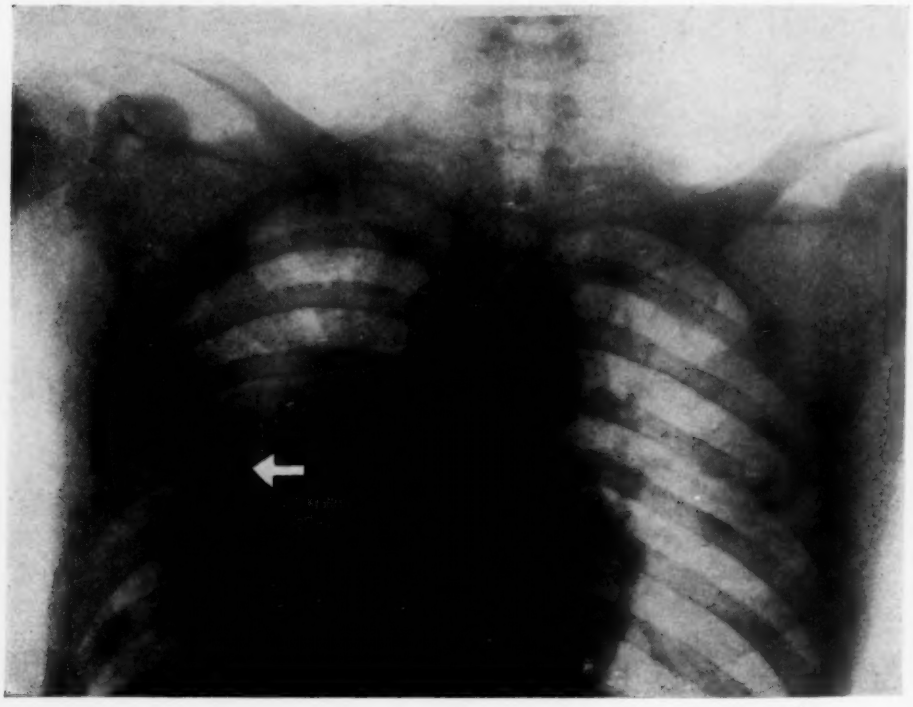

Fig. 1. *Case 7.* Male; age 17. Took a cold on 3/7/34. Entered the hospital on 3/9/34 with temperature of 101.4°, pulse 110, respiration 28. Film on 3/12/34 corresponds with clinical findings of left lower lobar consolidation.

pneumococcic infection of the bronchus causes the formation of a very tenacious fibrin-containing sputum which may readily narrow or completely occlude a large bronchus. With the occlusion of the main bronchus to a lobe, lobar atelectasis takes place, beginning at the periphery where the greatest number of alveoli are found, and progressing toward the hilus, while there follows a pneumococcic cellulitis proceeding peripherally from the hilus abetted by the negative pressure in the atelectatic area. Physical

* Presented before the Arizona State Medical Association June 8, 1934.

findings early in pneumonia would seem to substantiate this theory, as we frequently find the breath sounds diminished early in the disease with no definite signs of consolidation. Several roentgen-rays in our series demonstrate a condition which would seem to be best explained in this way. The toxic symptoms caused by the spread of the infection become more acute as the lung goes through the stage of red hepatization. If it happens that the occlusion of the bronchus is relieved early in the process, from the second to the fourth day, the disease takes an abortive form with an early crisis. The usual freeing of the occlusion occurs between the fifth and the eighth days with crisis, followed by more or less clearing of the lobe of its inflammatory

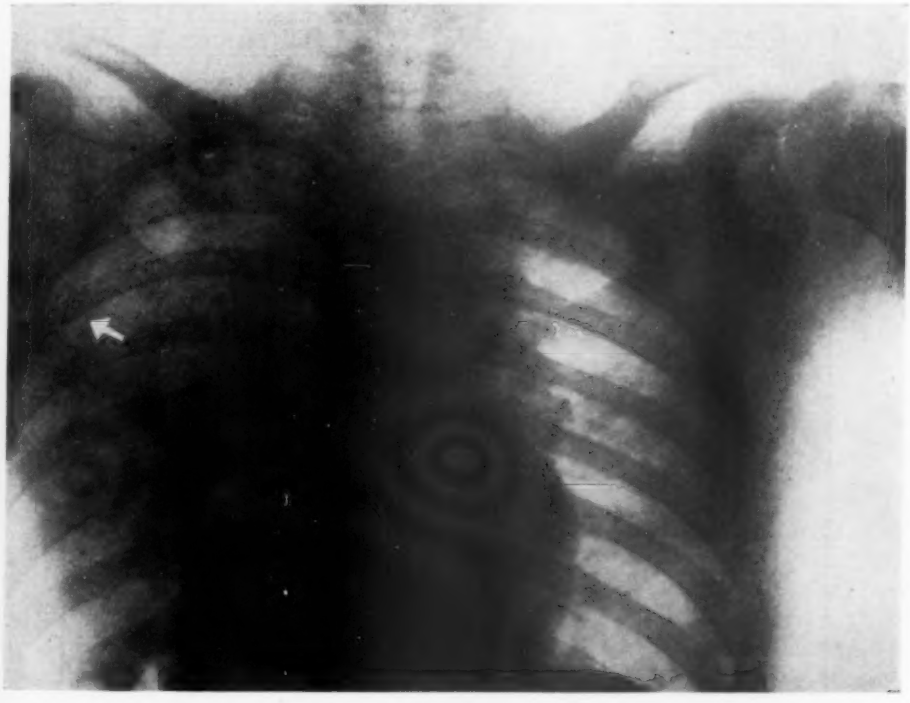

FIG. 2. *Case 7.* Arrows point out lung margins after introduction of 900 c.c. of air. Film shows partial consolidation of left lower lobe and some involvement of upper lobe. Crisis occurred 44 hours after initial pneumothorax treatment.

exudate, and leaving little subsequent damage. If relief of the obstruction of the bronchus is long delayed, then greater and greater changes in the lung parenchyma and bronchi take place—resulting in unresolved pneumonia, lung abscess or bronchiectasis. In accordance with this theory, clearing of the plugged bronchus precipitates the crisis and if this can be accomplished early, before all the smaller bronchi become tightly plugged, the severity of the illness may be aborted.

The very beneficial effect of artificial pneumothorax in massive atelectasis in tuberculosis has long been observed. The close similarity between

this condition and lobar pneumonia would indicate that perhaps equally good results might be obtained by this treatment in pneumonia. By collapsing a lung, it may be possible to free the mucous plug, thereby inducing an earlier crisis. Perhaps by lessening the negative pressure the spread of infection out from the hilus may be retarded. Accompanying the local diminution of blood volume incident to the pneumothorax it is reasonable to

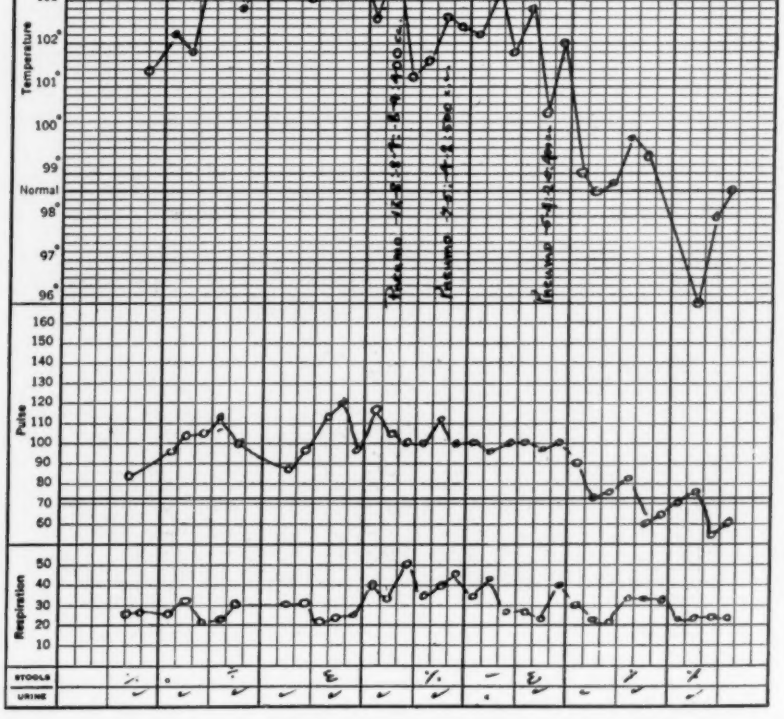

FIG. 3. *Case 7.* Temperature chart of severe pneumonia with delirium and severe pain in the left side, three days' duration. Pneumothorax —12—8: —8—4. 400 c.c. Patient continued delirious and after 12 hours a second treatment was given, —7—5: —4—2. 500 c.c. Previous severe pain relieved. General condition still not good; 24 hours later, —5—4: —2—0, 400 c.c. Temperature reached normal eight hours after this treatment. Total duration of high temperature four and three-quarter days. Critically sick pneumonia case given three pneumothorax treatments with uncomplicated recovery.

suppose that there will be a reduction in the absorption of toxins and bacteria into the circulation. On these theoretical considerations is based the rationale of the treatment.

Friedemann [2] in 1921 reported a series of nine cases treated with pneumothorax with no deaths. His conclusions were sufficiently favorable to encourage further study. Nothing further is reported until the work of Ibrahim and Duken [3] who in 1928 published a report of three cases and felt that the treatment had merit. Klotz [4] in 1928 reported several cases where pneumothorax was attempted but he was exceedingly skeptical as to its value. Coghlan [5] in 1932 reported six cases treated by pneumothorax and recommended the treatment very highly. Perlroth and Topercer [6] in the same year disagreed with practically all of Coghlan's conclusions and advised against the use of pneumothorax in pneumonia. Moorman [7] in a recent

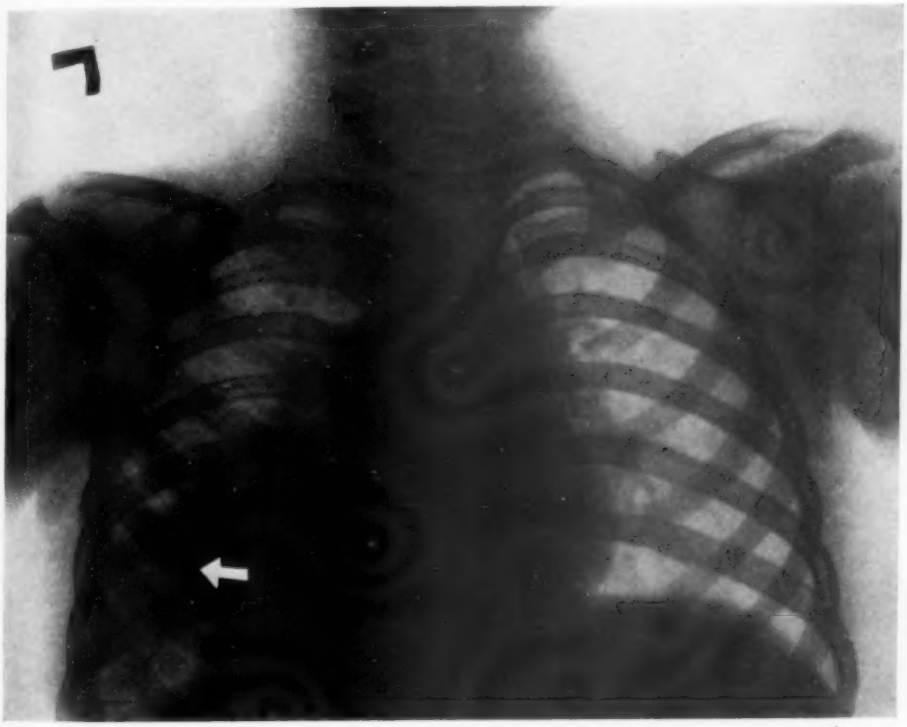

FIG. 4. *Case 15.* Arrow points to lower lobe consolidation, acute pneumonic process.

article reviews the literature and his own experience in this work and recommends its further use.

Behrend and Cowper recently reviewed the literature and reported 11 cases of lobar pneumonia with no deaths from pneumonia and two deaths from causes unrelated to the pneumothorax, one "an overwhelming septicemia," the other a "pneumococcic meningitis" occurring on the twenty-first day of the disease.

This paper presents our results with pneumothorax in 18 cases treated between January and April 1934.

In the accompanying chart our treated cases are grouped into adults and children with the dividing line at 12 years. The oldest person given pneumothorax was 36 years, the youngest three. There were eight adults and 10 children. Under associated diseases it is indicated whether these conditions were previously existing or were complications.

The days given as duration of pneumonic symptoms indicate the time before artificial pneumothorax was instituted. Usually pneumothorax was done promptly after the patient was seen by us, but occasionally a period of observation was necessary for definite diagnosis. Often it was very difficult to judge just when the pneumonic symptoms began, but usually high

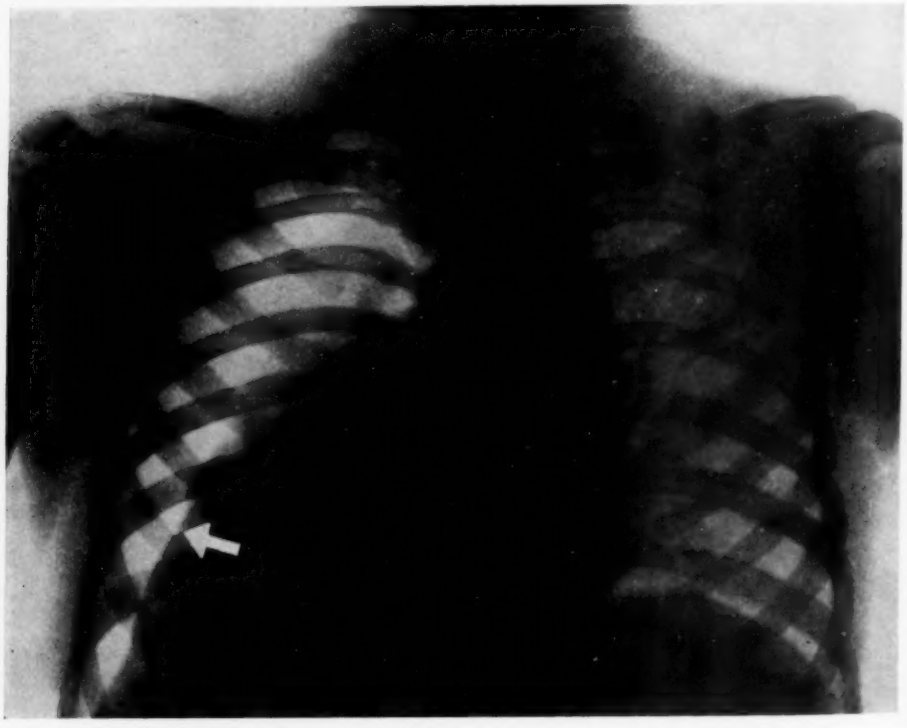

FIG. 5. *Case 15.* Pneumothorax established. No adhesions. Consolidation still present in collapsed lung.

temperature, chill and pain in the chest ushered in the pneumonia from a preëxisting respiratory infection.

Each case was proved to be lobar pneumonia by roentgen-ray, physical examination and clinical picture. Roentgenograms were taken before and after collapse was instituted, just before discharge from the hospital and, in many cases, another observation by fluoroscope or a roentgen-ray was taken about three weeks after discharge. The side involved seemed of no consequence, as the cases were equally divided between the two sides with equally good results. An estimate indicating the clinical severity from one

plus to four plus is given—the latter grade indicating one in which death seemed imminent. The temperature, pulse and respiration given were not averages but those actually recorded at the time of the initial pneumothorax.

The sputum was typed in those cases where it could be readily obtained but this was rarely possible from the children. All patients were under

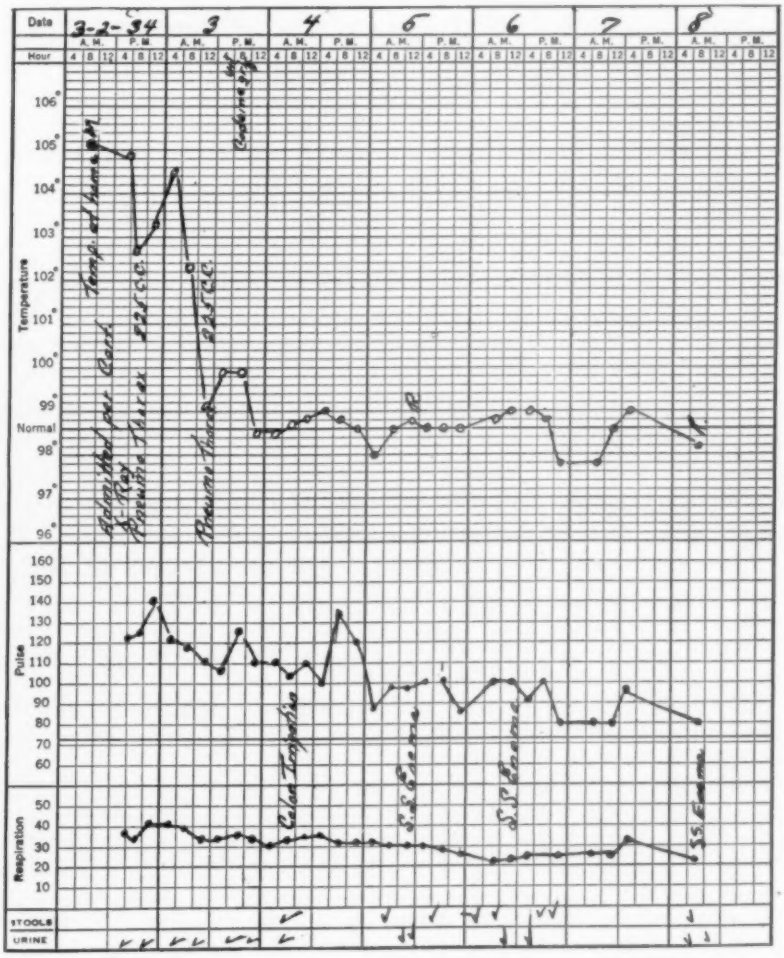

FIG. 6. *Case 15.* Temperature chart in case of previously strong, healthy boy six years of age, with left-sided pneumonia. Present illness began five days before admission to the hospital with symptoms of heavy chest cold. Severity of illness moderate. Pneumothorax —4—3:—2½—1, 225 c.c. Marked improvement in condition; 12 hours later —4½—2:—2—½, 250 c.c. Temperature reached normal 12 hours after second treatment and there was an uneventful recovery.

general nursing care. Since no sputum examined showed Type I pneumococcus a decision did not have to be made regarding use of serum.

Adhesions are noted—some of them demonstrated by the needle when two trials were necessary for injection of the air and some when roentgen-

rays were taken after pneumothorax. Only those patients in whom air was actually injected are included. There were two other patients in whom the lung was completely adherent. No air could be injected and these cases are not included in this report.

All patients complained of more or less pain in the affected side. In some there was a temporary increase after pneumothorax but it was always of brief duration. Cases marked with one plus indicate complete relief of moderate pain or moderate relief of severe pain, while two plus indicates a striking relief of severe pain.

In the first two charts, under the heading "pressures and amounts in c.c.," the first two numbers indicate the pressures before, and the last two numbers after injection. The figures are centimeters in the water manometer reading up or down from the neutral in one leg only. The time between injections is given in hours.

Under "fluid" is listed tea-colored fluid which remained sterile in two cases, while in the next column are listed the cases which went on to pus formation. Sterile fluid cases required no treatment and the presence of such fluid in no way affected convalescence.

The time from the original pneumothorax until the temperature became practically normal is listed. It might have been slightly elevated after that but the crisis had passed and that was the essential factor. The total duration of high temperature before the initial pneumothorax plus that afterward gives an idea of the duration of the disease when treated by this method and makes possible a comparison with the duration of pneumonia when untreated, or when treated in some other manner.

Case Reports

Case 1. W. C., well developed, well nourished, previously healthy male laborer, 20 years old. A cold for one week terminating in right-sided pneumonia of four days' duration, with severe pain. Sputum rusty—Type IV. Temp. 102.4°. Pulse 126. Resp. 32. Attempt at pneumothorax in posterior axillary line failed but a free space was found in front. Readings $-4-3$ before and $-3-2$ after injection of 300 c.c. of air. Marked relief from pain, and improvement in all symptoms. Eighteen hours later a second injection was given, $-3\frac{1}{2}-1:-1+2$, 300 c.c. There were quite marked adhesions but clinical results were excellent and temperature returned to practically normal in eight hours after first injection, making a total of four and one-third days pneumonia. It is perfectly possible that the second pneumothorax treatment was unnecessary.

Case 2. R. T., poorly developed and nourished male laborer. Had been somewhat asthmatic all his life—although not recently severe. Bronchitis for two weeks terminating in left-sided pneumonia three days before. Temp. 102.4°. Pulse 130. Resp. 36. Asthmatic symptoms, increased by pneumonia, somewhat alleviated by adrenalin. Pneumothorax, $-7-3:-5-2$, 400 c.c. Relief of sore spot in left chest. Temperature practically normal next day and in spite of doubtful necessity second injection was given, $-9-2:-2+1$, 350 c.c. Such a marked change in pressure after a small amount of air injected suggested diffuse adhesion of lung. Uneventful recovery of a moderately severe pneumonia in an asthmatic in four days.

Case 3. C. M., well developed, well nourished laborer 35 years old. Respiratory

CHART I

No. Age Type	Past History	Ass. Diseases	Clin. Severity	Days Sick Before Pnx.	Hrs. Fever After Pnx.	Temp. Pulse Resp.	Side Adhesions	Relief of Pain	Pressures and Amounts in c.c.	Fluid Pus	Results
					Adult Cases						
No. 1 20 IV	Healthy		++	4	8	102.4° 126 32	Right ++	++	−4−2; −3−2 : 300 18 hrs. −3½−1; −1+2 : 300		Good
No. 2 26	Asthmatic	Asthma	+	3	18	102.6° 136 36	Left +	+	−7−3; −5−2 : 400 24 hrs. −9−2; −2+1 : 350		Good
No. 3	Healthy		++	5	66	102.4° 110 34	Right ++	+	? ; −2½−½ − : 350 18 hrs. −3½−2; −1−½ : 400 24 hrs. −2½−½; −1−½ : 450		Good
No. 4 20 IV	Healthy		++	5	18	103.4° 105 34	Left −	+	−5−4; −3½−2½ : 400 18 hrs. −4−3; −3−2 : 450		Good

" Pnx.," abbreviation for Pneumothorax.

The average duration of pneumonia symptoms before pneumothorax was 3.5 days. The average total high temperature before and after pneumothorax was 5.5 days. There were no deaths. Excellent result in all patients.

CHART I—*Continued*

No. Age Type	Past History	Ass. Diseases	Clin. Severity	Days Sick Before Pnx.	Hrs. Fever After Pnx.	Temp. Pulse Resp.	Side Adhesions	Relief of Pain	Pressures and Amounts in c.c.	Fluid Pus	Results
					Adult Cases						
No. 5 32 III	Pneumonia in childhood. Healthy	Acute hem. nephritis	++	1	78	103° 126 40	Right +−	++	−4−3; −3−2 : 400 24 hrs. −5−3; −3−2 : 450 24 hrs. −3½−1; −1½−½ : 400 30 hrs. −4−2; −2½−1 : 400	Fluid Sterile	Good
No. 6 24	Healthy	Double otitis media	+	4	24	101° 100 38	Left +−	+	−8−7; −7−5 : 700	Fluid Sterile	Good
No. 7 17	Healthy		+++	5	44	104° 118 40	Left 0	++	−12−8; −8−4 : 400 12 hrs. −7−5; −4−2 : 500 24 hrs. −5−4; −2−0 : 400		Good
No. 8 36 IV	Healthy	Otitis media	++	1	12	104.4° 120 40	Right 0	+	−6−3; −5−2 : 700		Good

CHART II

No. Age Type	Past History	Ass. Diseases	Clin. Severity	Days Sick Before Pnx.	Hrs. Fever After Pnx.	Temp. Pulse Resp.	Side Adhesions	Relief of Pain	Pressures and Amounts	Fluid Pus	Results
					Childhood Cases						
No. 9 12	Pneumonia 3 times	Otitis media	+	4	168	103° 110 40	Left −	None	−4−3; −3−2 : 300 24 hrs. −3−1; −2−½ : 250	Fluid Spontaneous Pus	Empyema Recovery
No. 10 10	Pneumonia and asthma	Asthma	++	4	120	102.4° 138 36	Right +	+	−4−3; −3−2 : 275 24 hrs. −3+½; −2+2 : 200 Stopped because of asthma		Good
No. 11 11	Healthy		++++	4½	96	104.4° 133 32	Right +	+ but returned	−4−3; −2−1 : 300 24 hrs. −3−2; −1½−0 : 350 24 hrs. −3−1; −1+2 : 300 48 hrs. −2−½; −0+½ : 300 8 days sterile fluid	Fluid Spontaneous Pus	Empyema Recovery
No. 12 5	Healthy		+	4	60	103.4° 130 48	Left 0	+	−4−2; −2−1 : 250 18 hrs. −2−½; −1−1 : 175		Good

"Pnx.," abbreviation for Pneumothorax.

The average duration of pneumonia symptoms before pneumothorax was 4.7 days. Average total high temperature before and after pneumothorax 6.6 days, 60 per cent good results; recovery but with complications 20 per cent; 20 per cent mortality.

CHART II—*Continued*

No. Age Type	Past History	Ass. Diseases	Clin. Severity	Days Sick Before Pnx.	Hrs. Fever After Pnx.	Temp. Pulse Resp.	Side Adhesions	Relief of Pain	Pressures and Amounts	Fluid Pus	Results
					Childhood Cases						
No. 13 8	Healthy		+	3	32	103.6° 102 42	Right −	++	−4−2; −2−1 : 250 20 hrs. −3½−2; −2−1 : 300		Good
No. 14 6	Healthy		++	4	56	105° 128 32	Left −	+	−4−3; −2½−1 : 225 20 hrs. −3½−2; −1½−1 : 225 24 hrs. −2−½; −1½−0 : 250		Good
No. 15 6	Healthy		++	5	18	105° 130 42	Left −	++	−4−3; −2½−1 : 225 18 hrs. −4½−2; −2−½ : 250		Good
No. 16 3	Healthy	Buccal infection	++++	4	Not improved		Left ++	+ but returned	? ; +1+2 : 125 48 hrs. ? ; +1+2 : 100	Fluid Pus	Empyema Death
No. 17 11 III	Healthy	Otitis media	+++	8	Not improved	103.2° 130 46	Right ++	None	? ; +1+3 : 200 48 hrs. −1+1; +6+7 : 150	Fluid Spontaneous Pus Fistula	Empyema Death
No. 18 12	Double otitis media		+++	7	14	102° 120 40	Right +	+	−4−2; −2−3 : 175		Good

infection for one or two weeks developing into right-sided severe pneumonia five days before pneumothorax. Temp. 102.4°. Pulse 110. Resp. 34. Sputum Type II. Lung adherent in front but free space found behind. The first reading was questionable: —2½—1½, 350 c.c. followed by improvement. Eighteen hours later, —3½—2:—1—½, 400 c.c. In 24 hours the patient felt better, respirations were faster and the temperature was 103.2°. Third injection, —2½—½:—1—½, 450 c.c. Apparently he was embarrassed by this amount of air and the respiratory rate went up to 60. However, it dropped to normal in 18 hours and he was on the road to recovery. Total of seven and one-half days fever in a very ill man with three pneumothorax treatments.

Case 4. W. D., husky laborer, 20 years old, who had had a cold for about two weeks. Pneumonia for five days on left side with slight changes on the right side. Moderate pain. Temp. 103.4°. Pulse 105. Resp. 34. Sputum Type IV. Pneumothorax, —5—4:—3½—2½, 400 c.c. In 18 hours the temperature was normal and all symptoms had practically abated. Probably an unnecessary second injection was given, —4—2:—3—2, 450 c.c. Rather severe pneumonia with recovery in five and one-half days.

Case 5. E. G., well developed, well nourished clerk, 32 years old. Pneumonia in childhood but healthy as an adult. Epidemic of colds in his family with otitis media in two of family at the time of onset. At first no chest symptoms but acute nephritis with albumin and blood for five days, followed by well marked right-sided pneumonia of one day duration. Severe pain and cough; sputum Type III. Temp. 103°. Pulse 126. Resp. 40. Pneumothorax, —4—3:—3—2, 400 c.c. Pain was much relieved and 24 hours later, —5—3:—3—2, 450 c.c. The urinary symptoms were increasing, ankles showed pitting, blood pressure became higher and non-protein-nitrogen was found to be 132 mg. Temperature remained high. Twenty-four hours later, —3½—1:—1½—½, 400 c.c. Chest signs improved. Thirty hours later, —4—2:—2½—1, 400 c.c. Temperature dropped to normal and all symptoms except those relating to the urinary tract disappeared. Fluoroscopic examination showed a small amount of fluid in the pleural space. In spite of appropriate treatment starting before entrance to hospital the non-protein-nitrogen increased to 200 mg. This gradually receded and the patient is now free of symptoms. A case of severe Type III pneumonia, coincident with a severe acute nephritis, controlled by four pneumothorax treatments. The total duration of fever was five days. This would seem more favorable than was to be expected, as the patient went on to complete recovery with lung reëxpansion.

Case 6. C. J., well developed, well nourished male school teacher, 24 years old. Respiratory infection and otitis media for several days followed by a moderately severe left-sided pneumonia for four days. Roentgen-rays also showed slight shadows on right with consolidation of left lower lobe. Temp. 101°. Pulse 100. Resp. 38. On inducing pneumothorax two c.c. of sterile blood-tinged fluid were removed. The pressures were —8—6:—7—5, 700 c.c. Pain, quite severe before collapse, was much relieved. Temperature was lowered following pneumothorax, then assumed a low grade septic curve which was believed due to double draining otitis media, the chest symptoms having greatly abated.

Case 7. J. H., healthy male school boy, 17 years old. Left-sided pneumonia for five days. Condition very bad with a temperature of 104°–105° even with liberal use of aspirin. Temp. 104°. Pulse 118. Resp. 40. Pneumothorax, —12—8:—8—4, 400 c.c. Condition continued delirious and after 12 hours a second injection was given, —7—5:—4—2, 500 c.c. The previous severe pain was relieved, but his condition remained unfavorable. Twenty-four hours later, —5—4:—2—0, 400 c.c. The temperature became normal eight hours after this treatment. High fever for six and three-quarter days in a critically sick patient who made an uncomplicated recovery after three pneumothorax treatments.

Case 8. R. D., well developed, well nourished, healthy laborer, 32 years old. There was a moderately severe right-sided pneumonia of one day duration. Temp. 104.4°. Pulse 120. Resp. 40. Pneumothorax, —6—3:—5—2, 700 c.c. Great deal of pain in right chest for several days, relieved somewhat after pneumothorax. Temperature dropped almost to normal in 12 hours, but then rose to around 101.2° with otitis media present. Septic temperature for six days after collapse, right ear draining profusely. Moderation of chest symptoms suggested that fever was probably due to otitis media. Pneumonia was apparently terminated in 48 hours; right earache on second day; paracentesis on fourth day. Roentgen-ray showed complete recovery.

Case 9. F. L., poorly developed, undernourished school boy, 12 years old. There was an indefinite diagnosis of "pneumonia" in early childhood but his recent health had been fair. "Poor hearing" for years without definite diagnosis or treatment. Pneumonia of four days' duration, on left side. Pain in left chest quite severe with pleural friction rub and cough but confirmatory evidence was not as conclusive as in most cases. Temp. 103°. Pulse 110. Resp. 40. Pneumothorax, —4—3:—3—2, 300 c.c., was followed by some relief of pain. Twenty-four hours later, —3—1:—2—½, 250 c.c. Apparent improvement in chest symptoms but in meantime both ears required opening and drainage prolonged. The day after the last injection there was fluid in pleural space with undramatic spontaneous pneumothorax. Fluid rapidly turned to pus containing streptococci. When fluid was sufficiently thick a tube was inserted and this is still draining. Artificial pneumothorax in a moderately severe pneumonia terminating in spontaneous collapse, empyema and drainage. Recovery with minimal disability.

Case 10. L. C., fairly well developed and well nourished school boy, 10 years old. Father has pulmonary tuberculosis—present condition not known. The patient had pneumonia at the age of five months and has wheezed a little ever since. At the age of six years he developed what was called bronchial asthma, but a change in climate brought relief in a few months. He had recently been in good health. There was a moderately severe right-sided pneumonia of four days' duration—no asthma. Temp. 102.4°. Pulse 139. Resp. 36. Pneumothorax, —4—3:—3—1, 275 c.c. After the first treatment the temperature went to 106°. Twenty-four hours later he felt better, and a second treatment was given, —3—½:—2+2, 200 c.c. Complained considerably of adhesion pains. During the following days he became very asthmatic and was not relieved by medication. No further pneumothorax was given on account of asthma. The temperature continued high for five days after first pneumothorax treatment, then dropped and the patient made an uneventful recovery. Chest examination still showed many coarse râles on right with sonorous râles on both sides. This was a case of moderately severe pneumonia in an asthmatic with total duration of fever nine days.

Case 11. M. P., rather thin, poorly developed school girl, 11 years old. Right-sided pneumonia of four and one-half days' duration. Extremely ill with delirium for several days. Temp. 104.4°. Pulse 133. Resp. 32. Pneumothorax, —4—3:—2—1, 300 c.c. Not much change in condition, and a second treatment given 24 hours later, —3½—2:—½—0, 350 c.c. Pain in chest was relieved after this treatment but condition remained very serious. After another 24 hours, third treatment —3—1:—1+2, 300 c.c., followed by improvement. Two days later —2—½:0+½, 300 c.c. By this time her condition was apparently much better with less cough, no pain and the temperature almost normal. A few days later the pain in right chest returned and a sample of sterile fluid removed. Roentgen-ray examination indicated a spontaneous collapse had taken place at some time as she seemed to have more air in the chest than could be accounted for by treatments and there was change from previous roentgen-rays. However, pressures when sample was taken were —2½—1. Condition little changed for period of a few days when

temperature again rose to 102°–103° and remained so for a period of three weeks. Chest fluid still remained clear and sterile, but in a specimen 10 days later streptococci were found. This fluid gradually thickened and a tube drainage was instituted 55 days after the original pneumothorax. Condition thereafter was greatly improved. This was a case of very severe pneumonia given four pneumothorax treatments, with evidence of very few adhesions, terminating in spontaneous collapse and empyema.

Case 12. M. H., healthy child, five years old. Moderately severe pneumonia of left lung of four days' duration. Temp. 103.4°. Pulse 130. Resp. 48. Pneumothorax, —4—2:—2—1, 250 c.c. Not much change in condition after pneumothorax. Eighteen hours later, —2—½:—1+1, 175 c.c. Temperature was normal 32 hours after last treatment, and the child made an uneventful recovery. Moderately severe left-sided pneumonia in a child, given two pneumothorax treatments. Total duration of fever six and one-half days.

Case 13. E. J., healthy boy, eight years old. Moderately severe right-sided pneumonia with considerable pain of three days' duration. Temp. 103.6°. Pulse 102. Resp. 42. Pneumothorax, —4—2:—2—1, 250 c.c. Pain relieved. Twenty hours later —3½—2:—2—1, 300 c.c. Twelve hours later temperature normal. Uneventful recovery. A case of right-sided pneumonia of moderate severity; two pneumothorax treatments; total duration of fever four and one-half days.

Case 14. B. M., healthy girl, six years old. Left-sided pneumonia of four days' duration. Extremely ill. Temp. 105°. Pulse 128. Resp. 32. Pneumothorax, —4—3:—2½—1, 225 c.c. No improvement shown. Twenty hours later pneumothorax, —3½—2:—1½—1, 225 c.c. Condition unfavorable and low leukocyte count. Twenty-four hours later, —2—½:—1—0, 225 c.c. Temperature dropped quickly to normal after last treatment and the patient made an uneventful recovery. Severe left-sided pneumonia; three pneumothorax treatments; total duration of fever six and one-half days.

Case 15. F. W., strong healthy boy, six years old. Moderately severe left-sided pneumonia of five days' duration. Temp. 105°. Pulse 130. Resp. 42. Pneumothorax, —4—3:—2½—1, 225 c.c. Marked improvement in condition. Twelve hours later, —4½—2:—2—½, 250 c.c. Temperature was normal 12 hours after second treatment and the patient made uneventful recovery.

Case 16. E. M., healthy boy, three years old. Severe left-sided pneumonia with consolidation of entire lung shown by roentgen-ray. Patient almost moribund. Temp. 103.4°. Pulse 106. Resp. 55. No free space found on first attempt at pneumothorax. On second trial 125 c.c. given, after which readings were +1+2. Continued attempts at another treatment 24 hours later and 100 c.c. injected. Final pressure readings +1+2. Patient apparently became somewhat less toxic for about a week then an increasingly high septic temperature developed. Aspiration yielded pus. Roentgen-ray and fluoroscopic examination indicated more air in chest than had been given—possible spontaneous collapse. Condition became more toxic and tube was inserted one month after original pneumothorax. During the next month little change in condition except a severe buccal infection with whitish non-diphtheritic membrane. Died two months and five days after pneumothorax. This is an example of desperately ill pneumonia with almost a completely stuck lung; pneumothorax attempted with small amount of air injected, ending in empyema and death.

Case 17. D. N., well developed, plump girl, 11 years old. Right-sided pneumonia of eight days' duration; roentgen-ray showed basal fluid-like opacity. Temp. 103.2°. Pulse 130. Resp. 46. Pneumothorax was attempted in two places and lung was found completely adherent. Next day condition was so very critical that another attempt was made, 200 c.c. of air being given with final pressure reading of +1+3. Roentgen-ray showed a small pocket at base and 48 hours later as cough and general condition were very bad, another pneumothorax was given, —1+1:+6+7, 150 c.c. Roentgen-ray showed upper lobe adherent. Temperature gradually receded and

patient was clinically better over period of one week. Then she developed pus in pneumothorax pocket and roentgen-ray indicated a spontaneous collapse. When pus was washed out, a pleural bronchial fistula was demonstrated. Septic rising temperature necessitated insertion of tube 22 days after admission. Case of desperately ill right-sided pneumonia with markedly adherent lung crowded for pneumothorax and ending in spontaneous collapse, empyema, and death.

Case 18. A. A., healthy boy, 12 years old, who had recently recovered from otitis media. Right-sided pneumonia of seven days' duration. He was extremely ill, delirious, with a bad prognosis. Temp. 102°. Pulse 120. Resp. 40. Pneumothorax, —4—2:+2+3, 175 c.c. Temperature reached normal 14 hours after treatment and he proceeded to uneventful recovery. Total duration of fever seven and one-half days.

Discussion

The number of cases is small, but presents suggestive evidence. There appears to be a difference in the results obtained in the patients under the adult and childhood groupings. It happened that the adults had had pneumonia for an average period of 3.5 days, while the children averaged 4.7 days. This difference in the duration of the pneumonia before pneumothorax may have been a factor in the difference in the results obtained in the two groups.

The eight adult cases included five with greater or less adhesions, but in none was adequate collapse prevented. Of the 10 children listed, five had adhesions. To this number might be added two cases of pneumonia which were so adherent that no air was given; they were therefore not included in this group. This would make seven cases with adhesions out of 12 children in which pneumothorax was attempted. Of these adherent cases, numbers 16 and 17 were so adherent that only a small amount of air was injected under positive pressure. Both developed empyema and died. In retrospect, we should have desisted here even though the patients were in extremis. There were, therefore, four out of 12 which were so adherent that pneumothorax could not be given. The element of chance must be considered in viewing the difference between 100 per cent adequate collapse in adults and 66 per cent in childhood, but it probably does not account for the marked disparity.

There were no cases of spontaneous collapse nor of empyema in adults, while the latter developed in four out of 10 children. Three of these four definitely followed spontaneous collapse. The fourth might have done so but this is not certain. There were two instances of spontaneous collapse in cases without evident adhesions. Spontaneous collapse seems to be a real danger even in the absence of such an obvious warning signal as mounting pressure from adhesions. Just why it appeared more frequently in children than in adults is not clear, but it is perhaps due to a greater toughness of the pleura in adults. The technical difficulty in giving pneumothorax to an apprehensive child is self-evident and some of the children required two attendants to restrain them. However, the three spontaneous

cases were among the oldest children, two of them being 11 and the other 12 years old. They gave absolute coöperation during pneumothorax and there was no difficulty on account of movement of the patient. It would not have been surprising had spontaneous pneumothorax taken place in some of the smaller, very frightened children who struggled, but this was not the case.

There were two cases among the adults in which two c.c. of tea-colored sterile fluid were withdrawn before the first pneumothorax treatment. In both cases the fluid disappeared spontaneously. The four cases of empyema among the children all started with clear fluid which later turned into pus. In one case the fluid remained sterile for about a month before the first evidence of bacteria was found.

The presence of fluid or pus in six out of 18 cases, 33 1/3 per cent, as compared with cases of pneumonias treated otherwise, is striking. The figures of Rufus Cole of 9.2 per cent in 770 cases, or 6.25 per cent in 24,511 collected cases by Musser and Norris, need only to be quoted to see how excessively high is our incidence. Making all allowances one must suspect that the probability of empyema in pneumonia is increased by pneumothorax. Cases 16 and 17, in which great difficulty was encountered in giving the air, terminated fatally. Both were almost moribund when pneumothorax was attempted. Had we desisted when the difficulty was encountered, they would not have been listed with treated cases, and there would have been no mortality. By including them the mortality for all treated cases was 11 per cent. In the same hospitals at the same time were 15 cases of pneumonia treated without pneumothorax. In this group were six deaths, or a mortality of 40 per cent. The mortality figures given for pneumonia from year to year and decade to decade vary from 25 to 35 per cent. The mortality of our group has certainly been greatly reduced.

The possibility of hastening the crisis by pneumothorax is difficult to estimate accurately. In the first place the actual duration of the pneumonia previous to pneumothorax is often hard to determine. Furthermore, untreated cases of pneumonia vary greatly in their duration and many of our cases must have been near their crisis when first seen by us. In several of our cases the sharp drop in temperature within 24 hours was striking. If cases can be seen earlier it will be easier to determine this point. Our adults were seen after three and one-half days of pneumonia and the total length of pneumonia averaged five and one-half days, which would seem to be less than the average untreated case. Our children were seen after four and seven-tenths days and their average total time was six and two-thirds days which is probably not very different from the duration of cases treated by other means.

Pneumothorax seems definitely to help limit the pneumonic process as none of our cases spread into new non-affected lobes, whereas this is a common occurrence in untreated cases. Furthermore it seems to lessen the toxemia even when the crisis is not immediately brought about. The pa-

CHART III

No. Age Type	Day of Pneumonia												Result
	2	3	4	5	6	7	8	9	10	11	12	13	
No. 3 35 II				17850 80 49			N						Good
No. 4 20 IV					P 17000 91 24	P N							Good
No. 5 32 III	P 17600 78 34	P 14000 88 57	P 16000 78 42	P 18000 95 46	17600 93 48 N	15800 89 44	18000 90 30	17000 84 31	17000 76 21				Good
No. 6 24		26200 88		P	N								Good
No. 7 17			14150 80		P 13200 76	P 10100 83	9400 56 N						Good
No. 8 36 IV	P 36020 92 N from lungs	24500 92 T up ears	20050 87				N after ears						Good
No. 9 12			21000 91	P	P	EMPYE SPONTA	MA NEOUS						Empyema
No. 10 10				P 9600 74	P 6600 75	Asthma		N					Good
No. 11 11				P	P 8700 77 36	P 16050 85 53	11600 75	P 22200 80 38 Spont aneous	19600 79 38	17500 86 25	17300 50 28	15000 76 36	Empyema Recovery

No. Age Type	Day of Pneumonia												Result
	2	3	4	5	6	7	8	9	10	11	12	13	
No. 12 5			P 25800 90 52	P 30200 84 36	19850 85 N	25000 90 32	17000 79 28	16500 72 40	13200 75 20	9800 69 23			Good
No. 13 8			P 17200 90 42	P 19800 88 N	19200 89 28	12600 86 54			13200 76 31				Good
No. 14 6			11950 77 50	P 9500 76 40	P 9000 72 32 N	10600 80 42	15000 84 42	13400 89 38	5600 54 20	7400 36 22	6000 67 58	6600 40 24	Good Good
No. 15 6					P 24150 43	P 21000 26 N			12600 69 38	16400 58 30	17000 62 38		Good
No. 16 3				P 25400 87 58	P 15400 91 49	11800 78 62	11600 82 60	17800 91 40	14000 80 36	16000 66 46	13600 86 35	16400 70 40	Empyema and Death
No. 17 11 III							12800 88 39	P 21400 87 69	21600 68 60	P 26400 78 36	46800 87 56	23600 72 60	Empyema and Death
No. 18 12					18250 90		P 31500 93	N	Spontaneous 12850 69				Good

First Number—W.B.C.
Second Number—% Polynuclears
Third Number—% Non-Filament

P in corner—Pneumothorax
N—Normal temperature

tient feels better, appears brighter, eats with more relish and can be induced to take his fluids more readily. In practically all cases the breathing is easier, the rate lessened and the depth increased very definitely. This is probably explained by the fact that relief of pain is usually accomplished by separation of the pleural surfaces with air.

From the study of our pictures after absorption of the air and the apparent lack of late complications, there is a suggestion that we may expect fewer abscesses and less bronchiectasis afterward. Complete resolution shown by roentgen-ray took place in 10 to 14 days in a number of cases. The determination of this point will require study of a great many cases over a considerable length of time.

The technical difficulties of artificial pneumothorax increase as the age of the patient diminishes and it would seem advisable that one should not attempt the procedure unless he has had a fair experience in giving artificial pneumothorax especially if the patient is a very small child.

The accompanying chart shows the blood pictures with the high total white blood cell count, the high polynuclear count, and high non-filament count. The higher the non-filament count, the graver apparently is the prognosis. In only two patients did the count reach 60 per cent and both died. However, several very sick patients reached almost this figure during their worst period. Almost invariably the non-filament count recedes as the case becomes better. The white cell count continues high for some time after the crisis and usually the count was still much elevated when the patient was discharged from the hospital apparently well.

In conclusion we would urge that for a proper evaluation of pneumothorax in the treatment of pneumonia, the method be tried early in the course of the disease and the results checked carefully against a control series.

Conclusions

1. Artificial pneumothorax causes a marked reduction of pleurisy pain in lobar pneumonia, and it improves the depth of respiration.
2. It lessens the toxemia.
3. It seems probable that the duration of pneumonia is shortened, and that at times the crisis is brought about with dramatic suddenness.
4. In this series less difficulty was encountered from adhesions in adults than in children and there were fewer complications.
5. The danger of spontaneous collapse and empyema is increased in children.
6. Total mortality is decreased by use of pneumothorax and the chance of late complications such as abscess, bronchiectasis, or unresolved pneumonia, is probably reduced.
7. Spreading involvement to new lobes is checked.

We wish to thank Drs. C. C. Craig, J. M. Pearson, J. Drane, L. Kober, and H. B. Beauchamp for the reference of cases; Dr. W. W. Watkins for the roentgen-ray work; and the St. Joseph's and Good Samaritan Hospitals for their splendid coöperation.

REFERENCES

1. Corvllos, P. N., and Birnbaum, G. L.: Lobar pneumonia considered as pneumococcic lobar atelectasis of lung: bronchoscopic investigation, Arch. Surg., 1929, xviii, 190–241.
2. Friedemann, U.: Über Behandlung der akuten Lungentzüngang mit künstlichem Pneumothorax, Deutsch. med. Wchnschr., 1921, xlvii, 443.
3. Ibrahim, J., and Duken, J.: Zur Behandlung der kindlichen Pneumonie mit dem künstlichen Pneumothorax, Arch. f. Kinderh., 1928, lxxxiv, 241–249.
4. Klotz, M.: Die Anwendung des Pneumothorax bei Pneumonien im Kindesalter, Monatschr. f. Kinderh., 1929, xlii, 312–317.
5. Coghlan, J. J.: Treatment of acute lobar pneumonia by artificial pneumothorax, Lancet, 1932, i, 13–17.
6. Perlroth, S., and Topercer, M.: Behandlung der Pneumonien mit künstlichem Pneumothorax, Wien. klin. Wchnschr., 1932, xlv, 1508–1510.
7. Moorman, L. J.: Artificial pneumothorax in treatment of pneumonia, South. Med. Jr., 1934, xxvii, 233–237.

BEER IN THE DIABETIC DIET *

By Solomon Strouse, F.A.C.P., Samuel Soskin and Ben Vidgoff,
Chicago, Illinois

With the return of the legal use of alcoholic beverages in this country, we were faced by questions from many diabetic patients regarding the inclusion of these materials in their diet. The literature contains ample references to the use of alcohol and alcoholic beverages by diabetics, and we shall not attempt to review the bibliography, which is appended below for the convenience of those who are interested. Suffice it to say that, while the purer forms of alcohol have been generally considered to be permissible, and may even be of some therapeutic value in severe diabetes and in diabetic coma, opinions as to the use of beer have differed.

The objections to beer apparently rest chiefly on its relatively high content of grain extractives, which may give rise to sugar in the diabetic organism. It seemed to us, however, that the liberalization of the diabetic diet within recent years should render this a much less serious indictment than in the pre-insulin days. We therefore thought it worth while to study the effects of beer in the contemporary diabetic regimen.

Methods

Four male patients were maintained in the Max Pam Metabolism Unit throughout the entire experiment. After suitable preliminary and control periods, during which the diabetic status of each patient was stabilized and determined, beer was either added to the diet or substituted in the diet so as to leave the total caloric intake (except for the alcohol) unchanged. When beer was given, one 12 ounce bottle was allowed with each meal, so that the patient received 36 ounces per day.

In the two earlier experiments the so-called " 3.2 " beer was used; in the other two experiments beer of higher alcoholic content was given.† The following is the relevant portion of the analysis of the " 3.2 " beer as furnished us by the Wahl-Henius Institute, Chicago:

Specific gravity	1.01	
Alcohol by weight	3.01%	
by volume	3.86%	
Extractives (dissolved solids exclusive of alcohol)	5.37%	
Reducing sugar, as maltose		1.64%
Pentosans		0.42
Dextrins		2.30
Proteins		0.49
Ash		0.19
Acidity (as lactic acid)		0.12
Glycerin		0.21

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From The Max Pam Unit for Metabolic Research, Michael Reese Hospital, Chicago.
† In both cases the beer was of the " Rheingold " brand, kindly furnished us out of stock by the United States Brewing Company, Chicago.

The glucose equivalent of this beer, exclusive of the alcohol and ash and including 58 per cent of the protein, was calculated to be about 18 grams per bottle. The analysis of the stronger beer did not differ materially except for its alcoholic content (3.51 per cent by weight, 4.52 per cent by volume) and the same figure of 18 gm. carbohydrate equivalent per bottle was used in substituting it in the diet. The alcoholic portion of the beer was not included in these calculations because, as many workers have shown, alcohol is well tolerated and does not form sugar in the diabetic and we were therefore particularly interested in the non-alcoholic fractions of the beer.

Results

The results are given in table 1. The figures for urinary nitrogen and sugar excretion are the averages of daily determinations for the number of days specified in each period. The fasting blood sugar values are averages of analyses made twice a week during each period.

It may be seen that in the first patient (G. L.) the addition of 36 ounces of "3.2" beer to the diet was followed by no change in the sugar excretion but a surprising fall in the fasting blood sugar level. We are unable to explain this fall in the blood sugar, but that it is *not* due to some therapeutic action of the beer seems clear from the next patient (R. T.) in whom the addition of the same amount of beer caused a slight rise in both the fasting blood sugar level and the glycosuria. Furthermore, the last control period on patient R. T. shows that he tolerated the addition of an equivalent amount of carbohydrate to his diet, quite as well and perhaps better than when beer was added. The fourth patient (E. A.) showed a definite increase in both the blood sugar level and glycosuria when the "strong" beer was added to the diet.

The substitution of the "strong" beer for an isocaloric amount of carbohydrate in the diet of the third patient (C. W.) produced a hardly significant rise in the fasting blood sugar level and in the glycosuria. In the fourth patient (E. A.), in whom the addition of the "strong" beer had raised the blood sugar level and the glycosuria, both values returned towards the control figures when the same amount of beer was substituted in the diet.

Since in our calculations no account has been taken of the caloric value of the alcohol contained in the beer, it is evident that our patients were able to utilize these additional calories without forming extra sugar and without requiring more insulin. This extra source of calories amounts to the not inconsiderable sum of about 228 calories per day for the "3.2" beer, and 265 calories per day for the "strong" beer. While this source of energy may be of no special value in treating our particular cases, it might conceivably prove to be of practical importance in cases which are just on the borderline as regards their need for insulin to handle an adequate caloric intake.

TABLE I

Patient	Period of Experiment	Duration of Period	Diet						Daily Insulin	Fasting Blood Sugar	24 Hour Urine Excretion	
			P.	F.	C.	Cals.	Beer	Total Cals.			Nitrogen	Sugar
		Days	Gm.	Gm.	Gm.				Units	Mg. %	Gm.	Gm.
1. G. L.	Control	12	60	150	100	1990	0	1990	30	203	3.82	0.55
	Beer ("3.2")	21	60	150	100	1990	Added	2206*	30	87	5.86	0.66
2. R. T.	Control	16	70	100	125	1680	0	1680	10	143	11.27	4.08
	Beer ("3.2")	12	70	100	125	1680	Added	1896*	10	166	10.76	7.93
	Control	15	70	100	125	1680	0	1680	10	150	10.82	2.16
	Control	10	70	100	179	1896	0	1896	10	140	9.20	3.36
3. C. W.	Control	9	75	120	120	1860	0	1860	90	229	9.12	3.51
	Beer ("strong")	7	75	120	66	1644	Substituted	1860*	90	255	8.54	6.82
4. E. A.	Control	19	70	100	125	1680	0	1680	60	180	9.63	2.06
	Beer ("strong")	9	70	100	125	1680	Added	1896*	60	241	9.50	8.27
	Beer ("strong")	20	70	100	71	1464	Substituted	1680*	60	193	9.80	4.28

* These figures do not include the caloric value of the alcohol, which amounts to 228 calories for the "3.2" beer and 265 calories for the "strong" beer per day.

Summary and Conclusions

Our results show no effects of beer, either harmful or beneficial, in the diabetic diet. To the extent that the alcohol contained in the beer may be utilized without forming sugar and without requiring additional insulin, beer may offer an advantageous source of extra calories in some cases. Our results indicate that, while some patients may probably take moderate amounts of beer in addition to their diet, it is wise to substitute it in isocaloric amounts (exclusive of the alcohol) for other foodstuffs in the diet, as one would do in dealing with any other special article of food.

We are indebted to the Department of Chemistry for aid with the chemical determinations.

BIBLIOGRAPHY

Abderhalden, E.: Bibliographie der gesamten wissenschaftlichen Literatur über den Alkohol und den Alkoholismus, 1904, Urban and Schwarzenberg, Berlin and Vienna.

Allen, F. M., and Wishart, M. B.: Alcohol in the diabetic diet, Jr. Metab. Res., 1922, i, 281–306.

Benedict, H., and Török, B.: Der Alkohol in der Ernährung der Zuckerkranken; experimentelle Untersuchungen, Ztschr. f. klin. Med., 1906, lx, 329–348.

Blatherwick, N. R., Maxwell, L. C., and Long, M. L.: Effect of oral administration of alcohol upon blood sugar of rabbits, Am. Jr. Physiol., 1924, lxvii, 346–347.

Bornstein, A., and Loewy, A.: Untersuchungen über den Alkoholumsatz beim Menschen, Biochem. Ztschr., 1927, cxci, 271–292.

Burdi, I.: Experimentelle Untersuchungen über den Einfluss einiger Arzneimittel auf die Blutzuckerkonzentration, Ztschr. f. d. ges. exper. Med., 1930, lxxi, 480–488.

di Natale, A.: Comportamento delle sostanze riducenti volatili del sangue dei diabetici e loro rapporto con la glicemia, la glicosuria e l'acetonuria, Policlinico (sez prat.), 1930, xxxvii, 833–836.

Edkins, N., and Murray, M. M.: Sugar tolerance and alcohol, Jr. Physiol., 1931, lxxi, 403–411.

Fuller, L. S.: Immediate influence of alcohol ingestion upon diabetic glycosuria and blood sugar, Jr. Metab. Res., 1922, i, 609–617.

Gavrila, J., and Sparchez, T.: Action de l'alcool sur la glycemie, Compt. rend. Soc. de biol., 1928, xcviii, 65–66.

Himwich, H. E., and others: Metabolism of alcohol, Jr. Am. Med. Assoc., 1933, c, 651–654.

Hunt, T. C.: The action of alcohol upon the blood sugar in diabetes mellitus, Lancet, 1930, i, 121–124.

Joslin, E. P.: The treatment of diabetes mellitus, 1928, Lea and Febiger, Philadelphia.

Labbé, M., Nepveux, F., and Monzaffer Chevki: Effet de l'alcool sur la glycémie et sur les échanges respiratoires chez les sujets sains et les diabétiques, Arch. d. mal. de l'app. digestif., 1929, xix, 1053–1058.

Leclercq, F. S.: Overnutrition with fat and alcohol in severe diabetes, Jr. Metab. Res., 1922, i, 307–317.

Lepine, R.: Influence of alcohol on sugar content of dog's blood, Rev. de Med., 1916, xxxv, 506.

Mellanby, E.: Action of alcohol on the human economy, Brit. Med. Jr., 1922, ii, 195–199.

Moretti, P., and Bellinghieri, P.: Alcool e glicemia nei soggetti non diabetici e nei diabetici, Rassegna di terap. e. pat. clin., 1930, ii, 465–470.

Mosenthal, H. O., and Harrop, G. A., Jr.: Comparative food value of protein, fat, and alcohol in diabetes mellitus as measured by nitrogen equilibrium, Arch. Int. Med., 1918, xxii, 750–758.

NAUNYN, B.: Der Diabetes mellitus, 1898, Alfred Holden, Vienna.

NEUBAUER, O.: Über die Wirkung des Alkohols auf die Ausscheidung der Azetonkörper, München. med. Wchnschr., 1906, liii, 791.

NITZESCU, I. I.: Action de l'alcool sur la glycémie dans la diabète experimental, Compt. rend. Soc. de biol., 1927, xcvii, 1104–1105.

NOORDEN, K. VON: Die Zuckerkrankheit und ihre Behandlung, 1912, August Hirschwald, Berlin.

SOUTHGATE, H. W.: Effect of alcohol, under varying conditions of diet, on man and animals, with some observations on the fate of alcohol in the body, Biochem. Jr., 1925, xix, 737–745.

STÄUBLI, C.: Beiträge zu Pathologie und Therapie des Diabetes, Deutsch. Arch. f. klin. Med., 1908, xciii, 107–179.

THE DIAGNOSIS OF CARDIAC ANEURYSM WITH REPORT OF TWO CASES *

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There are comparatively few reports of aneurysms of the heart in American literature. The condition is not common, and most of the reported cases are foreign. In a review of 12,000 autopsies Lucke and Rea [1] found 321 instances of all aneurysms. Of this number only 15 were cardiac, indicating an incidence of 1.25 per 1,000 autopsies and 4.64 per cent of the total number of aneurysms.

According to Sternberg [2] 84.6 per cent of aneurysms of the heart are produced by coronary artery disease. Because of the greater incidence of coronary disease in males, cardiac aneurysms occur more frequently in this sex. In a review of 112 cases Hall [3] found 74 per cent in males and 26 per cent in females. Sternberg found 65 per cent in males and 35 per cent in females. Its occurrence is almost entirely confined to the arteriosclerotic age, if we disregard the rare congenital aneurysms and those produced in the course of endocarditis, especially the subacute bacterial form, as reported by Wilson.[4] There are exceptional cases in which the condition was produced by injury. Preble [5] reported one in a boy, 10 years old, who developed an aneurysm of the left ventricle following a bullet wound; Joachim and Mays,[6] another in a man 25 years old, in whom at post mortem a calcified aneurysm was found on the anterior wall of the left ventricle, which they assumed was due to an injury of the chest at 12 years of age.

Most of the reported instances have neither been diagnosed nor even suspected during life and were accidental postmortem findings. In a series of 300 such cases, Pletnew [7] found that only six (0.5 per cent) were diagnosed during life. There are a few other reported cases that were diagnosed or suspected before death. Most diagnoses were made by radiologic means. Thus Steel [8] reports six cases, all undiagnosed clinically, five of which were detected by roentgen-ray, and three proved by autopsy. One was not shown by roentgen-ray but was found at autopsy. Lenk,[9] Albrecht,[10] Groedel,[11] Branchi,[12] and Fogel [13] report single cases that were diagnosed radiologically but not clinically.

There are a few cardiac aneurysms reported that were diagnosed clinically. Some of these had very marked signs such as bulging pulsations that could not be missed. In others the diagnosis was based on careful examination and the detection of unusual signs suggestive of the condition. Apparently the first case so diagnosed was that of Remlinger.[14] Later Voelcker [15] reported two cases, Queralto [16] one, Sternberg [2] one, Harvier and

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From the Department of Medicine, Coney Island Hospital, Brooklyn, N. Y.

Caroli [17] one, Smith [18] one, Pletnew [7] two, and Lutenbacher [19] two cases that were diagnosed clinically and confirmed at autopsy. Christian and Frik [20] reported a case diagnosed by roentgen-ray but the autopsy findings showed the aneurysm to be in a different location from that indicated. They conclude that it is impossible to make a diagnosis of cardiac aneurysm by physical findings.

The reason for the failure in diagnosis is that there are no constant clinical signs characteristic of the condition. The predominant symptoms are merely those of the late stages of coronary artery disease. In many instances, such as in the cases reported by Hughes,[21] Wilson [22] and others, there were no noticeable symptoms present until death caused by rupture of the aneurysm.

Because of the rarity of the disease and the greater rarity of a correct clinical diagnosis, we wish to report the following two cases which were diagnosed clinically. The roentgen-ray findings in one case were negative and in the other case indicated an aneurysm. In both cases the autopsy findings confirmed the diagnosis.

Case Reports

Case 1. S. M., an Italian laborer, aged 33 years, entered the Coney Island Hospital February 7, 1934 and died March 1, 1934. On entrance he presented a right hemiplegia and loss of speech. His family history was essentially negative, as was his past history until two months before he came to the hospital. At that time the patient was suddenly seized with severe precordial pain, marked dyspnea, cyanosis and vomiting. He remained in bed several days. Since that time he had been having repeated attacks of precordial pain which occurred with increasing frequency. No signs of decompensation developed. About a week before he was seen by us the patient had an attack of severe cough, with bloody (?) expectoration, and fever. The night before, a doctor had seen him and made a diagnosis of "resolving pneumonia." At 10:00 a.m. on February 7, 1934 the patient woke up with a hemiplegia and was unable to speak. He also developed some dyspnea. He entered the hospital at 2:00 p.m. on that day. On examination he was fully conscious and cooperative but unable to speak. He was somewhat drowsy but could be readily aroused. He was moderately dyspneic and cyanotic. His pupils reacted to light and in accommodation. The ears and nose were negative. The tongue was moist, covered with a brownish fur and protruded in the middle line, the throat slightly reddened. There was paralysis of the lower two-thirds of the right side of the face and of the right arm and leg with exaggerated deep reflexes and positive Babinski sign on that side. The heart was enlarged to the left, had a gallop rhythm, and the sounds were hardly audible. A soft systolic murmur was heard at the apex which was not transmitted to the axilla. The lungs showed dullness on the right side posteriorly from the angle of the scapula to the base, with numerous crepitant râles and vesicular breath sounds. There were also some râles at the left base posteriorly. The abdomen was relaxed and no tenderness was encountered. The liver edge was palpated about four cm. below the costal margin, the spleen not felt. The genitalia were normal and nothing unusual was noted on rectal examination. No lymphadenopathy was present. There was no peripheral edema. The temperature on admission was 101.4° F., pulse 104 and respirations 40. Blood pressure was systolic 110 over diastolic 90. The blood: red blood cells numbered 3,000,000; white blood cells 12,600 with 66 per cent polymorphonuclears; hemoglobin 58 per cent (Sahli). Wassermann test was negative. The urine and the blood chemistry examinations showed nothing abnormal.

On February 8, 1934 the patient was definitely cyanotic, his breathing was rather harsh, and his heart was enlarged to the left with marked prominence and heaving impulse at the apical region. A soft systolic murmur was heard at the apex, accompanying a very weak first sound and there was a presystolic gallop rhythm. We made a diagnosis of recurrent coronary occlusion; apical aneurysm of the heart; mural thrombi in the left ventricle with embolism to the left middle cerebral artery; possible old pulmonary embolism with infarction; congestive heart failure.

In a few days the general condition of the patient improved, and he became less cyanotic. At the end of a week he was able to articulate a few words and recovered some power in the right leg. The heart sounds also improved slightly. Throughout the rest of his stay in the hospital his temperature ranged from 98.6° F. to 102° F., pulse 80 to 110, and respirations 18 to 36. The blood pressure varied from systolic 100 to 106, diastolic 88 to 90. Subsequently he had repeated attacks of precordial pain with occasional dyspnea and slight cyanosis. On February 22 he had an attack of nausea and vomiting which persisted intermittently until death. The pain in the precordium became very severe and constricting on the twenty-third, when he became stuporous and exhibited Cheyne-Stokes respiration with prolonged apneic periods. His color was definitely ashen. The heart findings were practically the same, except that the sounds were more muffled. He continued to vomit at intervals and the precordial pain, which later radiated to the abdomen, became progressively worse until his death, March 1, 1934.

A roentgen-ray (portable) examination was made on February 23 (figure 1) and was commented on as follows: "The heart is rather markedly enlarged, particularly to the left, the enlargement being predominantly left ventricular. There is otherwise no unusual deformity of the cardiac shadow. The arch is narrow. The mediastinum and diaphragm appear to be normal. There is a marked degree of pulmonary congestion present with slight pleural thickening, particularly between the upper and middle lobes of the right lung. There is no pulmonary infiltration."

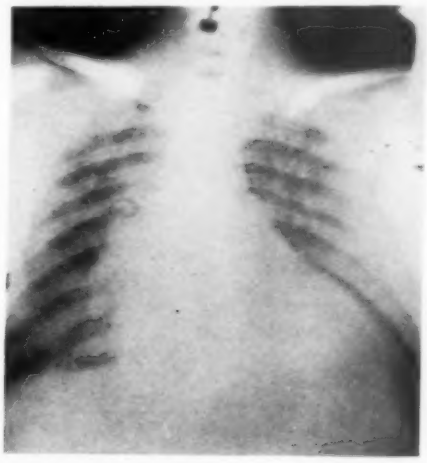

FIG. 1. Roentgen-ray, antero-posterior position. Heart diffusely enlarged but no deformity of the cardiac shadow seen.

Electrocardiographic tracings (figures 2, 3, and 4) were made on February 7, 14 and 23. The general features in all three leads were practically the same. There was a regular sinus rhythm; auriculo-ventricular and intraventricular conduction time were normal; slight slurring of the QRS in all leads, major QRS deflection in the

2–7–34

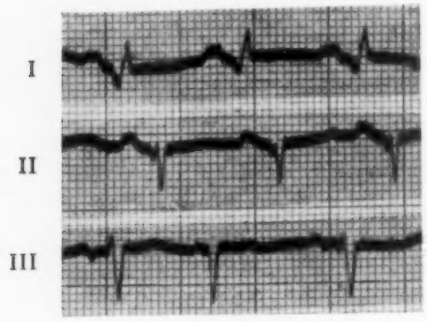

FIG. 2.

2–14–34

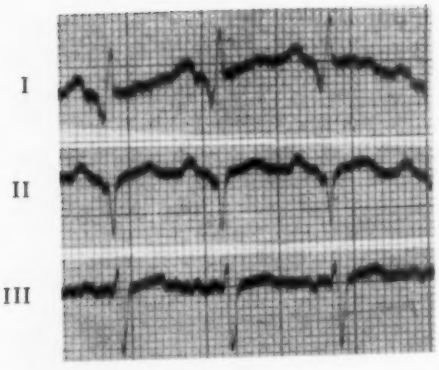

FIG. 3.

2–23–34

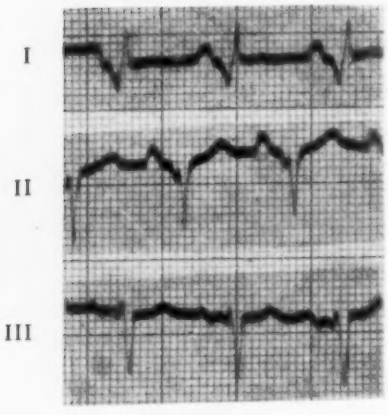

FIG. 4.

first lead in the form of R-wave and in the second and third leads in the form of S-wave in all tracings. There were, however, some slight variations in the T-wave in the various tracings. On February 7 the T-wave in the first lead was isoelectric, in the second lead it was nearly isoelectric, and in the third lead it was of low voltage. On February 14 there was a tendency for the T-wave in the first lead to be slightly positive, in the second and third leads it was definitely positive, but of low voltage. On February 23 the positivity of the T-wave was more pronounced. The voltage of the QRS complexes in all leads was somewhat higher on February 14 and 23 than on February 7. There were also some minor variations seen in the P-waves in the two subsequent tracings as compared with the first tracing. In general, the electrocardiograms showed evidence of marked myocardial disease of a rather chronic nature, inasmuch as it did not show progressive changes that are often seen in acute coronary occlusion.

Necropsy was performed by Dr. Harold Fink. Section of the head was not permitted. The left pleural cavity contained about 200 c.c. of straw-colored fluid. The lungs showed marked congestion. The heart (figure 5) weighed 450 gm. The pericardium was adherent to the lower half of the anterior surface of the left ventricle. There were numerous petechial hemorrhages over the posterior surface of the epicardium. The tricuspid valve was of usual appearance, and the right auricle of average size. The wall of the right ventricle measured 0.4 cm. in thickness. The septum bulged into the right side of the heart. The pulmonary vessels were of average size, and the branches of the artery showed no obstruction nor thrombus formation. The pulmonary valve leaflets were normal. The wall of the left auricle was smooth. The mitral valve was translucent. The chordae tendineae were not unusual. The wall of the left ventricle varied in thickness from 1.0 cm. to 0.3 cm. (at the apex). The lower two-thirds presented a marked sacculation, the size of a medium-sized orange, and filled with postmortem clot. There were several pieces of organized thrombi in the interstices of the trabeculi. The aortic cusps showed moderate atheromatosis and slight loss of elasticity. The commissures and valve

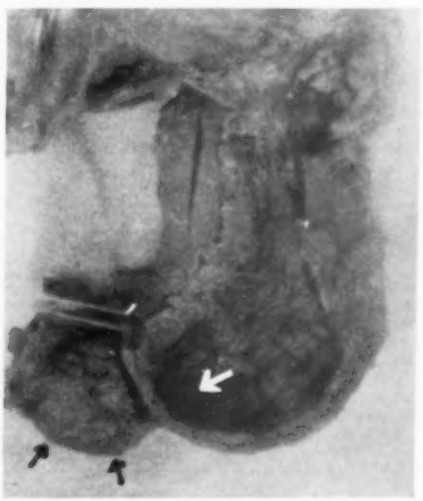

FIG. 5. Gross specimen of the heart showing the aneurysm (arrows).

edges were of average appearance. The aorta was diffusely atheromatous. The left coronary artery was completely occluded in its entire course beginning about 0.2 cm. from its origin. The circumflex branch was partly patent but the anterior descending

branch showed complete organization. The right coronary artery showed a marked diffuse atheromatosis with moderate narrowing of the lumen. The superior and inferior venae cavae were patent throughout.

The liver weighed 1500 gm. and had a marked nutmeg appearance with large irregular confluent light yellow areas. The spleen weighed 180 gm. It was firm, the follicles were prominent and there was moderate fibrosis, but no infarct. The combined weight of the kidneys was 380 gm. The capsules stripped with moderate ease, leaving gross scarring of the surface. There was a moderate shading of the cortex into the medulla. There was an increase of pelvic fat. The renal arteries were slightly atheromatous. No other organs showed anything unusual.

Microscopic sections of the heart showed brown atrophy, loss of striations of muscle fibers and marked diffuse fibrosis. In some areas individual nuclei showed karyokinesis and karyolysis. In the liver there was congestion of the central portion of the lobules with atrophy of liver cells. Kidney sections showed hyalinized glomeruli and areas of cloudy swelling and hyaline casts in the tubules.

Case 2. S. W., a Russian storekeeper, aged 58 years, was admitted to the Coney Island Hospital on February 22, 1934 and died on April 18, 1934. The essential features in the family history were that a brother died at 56 years of age of gangrene of both feet, one son died at 29 years of pneumonia, one was operated on at 26 years for nephrolithiasis, and a third son died at the Kings Park Hospital for the Insane. His wife at the time of his illness was confined to Kings Park Hospital. He had measles and scarlet fever in childhood and acute bronchitis at 17 years of age. He had suffered an attack of severe precordial pain 15 years before and some palpitation and dyspnea on exertion a week before the present illness. He had smoked about 15 cigarettes per day from early youth.

Present illness: On February 21, 1934 at about 10:30 p. m. while drying dishes at home, he was suddenly seized with a severe vise-like constricting precordial pain radiating upward to the shoulders and down both arms, more to the left than to the right. The attack lasted about 10 minutes and subsided. He went to bed but was awakened one hour later by a recurrence of the same pain. This time it was so severe that he thought he was going to die. This attack also gradually passed off only to return with still greater severity at 4:30 a.m. on February 22. A physician was called, who administered half a grain of morphine and advised hospitalization. The pain was still continuous at 5 a.m. when he came to the hospital, and persisted for several hours afterward.

On physical examination the patient appeared acutely ill. His color was ashen and expression anxious; he was not particularly dyspneic. The pupils were equal and regular and reacted to light and in accommodation. The mouth showed pyorrhea alveolaris and many carious teeth. The throat was slightly injected and the tongue dry. The neck showed no adenopathy and no visible pulsation. There was considerable peripheral arteriosclerosis. The heart was moderately enlarged to the left. The first sound was diminished in intensity at the apex and was more intense at the fourth left costosternal junction. The pulmonic second sound was greater than the aortic second sound. The ventricular rate was about 90 and the rhythm was regular. No murmurs were heard. The lungs showed normal resonance and breath sounds. The abdomen was not remarkable. No peripheral edema was present and the reflexes were normal. The temperature on admission was 101.6° F., pulse 86, respirations 20. The blood pressure was systolic 124, diastolic 80. The blood: red blood cells 2,000,000; white blood cells 23,000 with 68 per cent polymorphonuclears; hemoglobin 42 per cent (Sahli); Wassermann test was negative. The urine contained one plus albumin but was otherwise normal. The blood chemistry examinations were normal. The diagnosis was acute coronary occlusion.

On February 23 a few inspiratory crepitant râles were heard at the left base. The other findings were the same as on the previous day. A teleroentgenogram on

that day was reported: "The heart is moderately enlarged, particularly to the left of the midline. There is slight prominence of the left upper cardiac border. There is some elongation of the aorta. The mediastinum, diaphragm and ribs appear normal. The shape of the heart is not characteristic of any valvular lesion. The lung fields are aerated. There is a slight degree of pulmonary congestion with evidence of chronic bronchitis and slight pleural thickening. There is no significant parenchymal lung infiltration. There are a few areas of discrete fibrosis of the upper lobe. Diagnosis: Cardiac enlargement; elongation of the aorta; pulmonary congestion."

An electrocardiogram (figure 6) on the same day showed slight elevation and coving of the S–T segment in the first lead with negative T-wave formation; elevation and coving of the S–T segment in the second lead with beginning negative T-wave formation; also elevation and coving of the S–T segment in the third lead with beginning negative T-wave formation; there is very faint slurring of the QRS complexes in all leads and negative P-wave in the third lead.

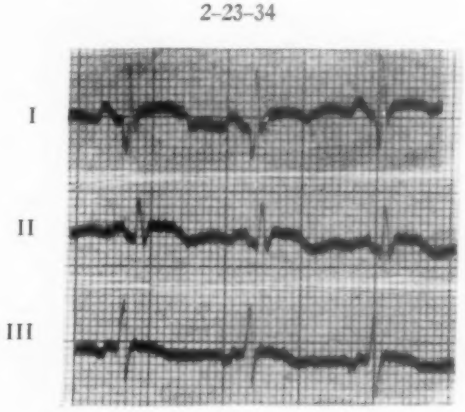

FIG. 6.

The precordial pain gradually subsided and his condition seemed to be slightly improved during his first three weeks in the hospital. His temperature ranged from 98° to 101.8° F., pulse 70 to 100, and respirations 18 to 24. Blood pressure ranged from systolic 100 to 122, diastolic 64 to 82. On March 12 there was some shortening of the first sound, assuming more or less of a valvular quality. Size and configuration of the heart were about the same.

Other electrocardiograms were made on March 12 and March 21, 1934. Because they were similar to each other, only the latter (figure 7) is herewith reproduced. This tracing shows diminished voltage of the QRS complex in the first lead as compared to the one of February 23 with markedly negative T-wave formation in the first and second leads and isoelectric T-wave in the third lead with return of the S–T segment in all leads to the isoelectric level. The S-wave in the third lead seen in the first tracing has disappeared and there is a definite Q-wave in the tracing of March 21. There is also some slurring of the base of the descending limb of the R-wave in the third lead which is not present in the previous tracing. The P-wave in the third lead which was previously negative has now become diphasic.

On March 17 the patient developed a sore throat and his temperature rose to 102° F. His general condition became slightly poorer. The fever thereafter persisted on a somewhat higher level ranging from 100.6° F. to 103.4° F. throughout the fifth and sixth weeks of his stay in the hospital. The cardiac findings remained practically the same although there seems to have been some improvement in the quality of the first

sound. On April 2 percussion of the heart dullness indicated some bulging of the left border of the heart above the apex. There was a presystolic gallop rhythm with marked diminution in intensity of the first sound at the extreme edge of cardiac dull-

3-21-34

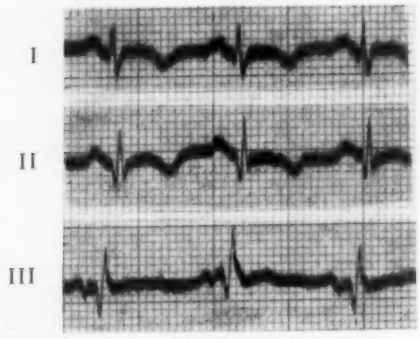

FIG. 7.

ness. Both bases of the lungs showed diminished breath sounds with numerous inspiratory bubbling râles. Our diagnosis at that time was left ventricular aneurysm near the apical region with possible mural thrombi; progressive myocardial damage; congestive heart failure.

4-16-34

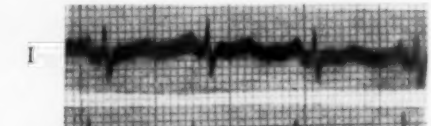

FIG. 8.

Further electrocardiograms were made on April 2 and again on April 16. Because of their similarity, only the latter (figure 8) is herewith reproduced. This tracing shows marked slurring of the QRS complexes in the first lead; positive T-wave in the first lead; isoelectric T-wave in the second lead and negative T-wave in the third lead; all of which differ from the tracings taken on March 21 and indicate progressive myocardial changes. At our suggestion another teleroentgenogram (figure 9) was ordered on April 3, with the following report: "The film shows practically the same cardiac findings as previously described. At this time the bulge in the left cardiac border, which was previously noted, is still seen. This prominence is slight and lies in the upper portion of the left ventricular border. The appearance is very suggestive of a ventricular aneurysm, particularly since it is present on the previous film as well as on this one."

In view of these findings, Dr. Emanuel Mendelson, the radiologist, made a fluoroscopic examination in the supine position. His findings were: "The heart is enlarged to the left; amplitude of contractions diminished; the prominence of the upper portion of the left ventricle is seen as noted on film examination and the wall

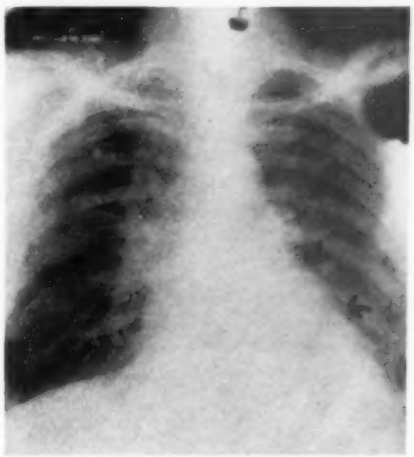

FIG. 9. Roentgen-ray in the antero-posterior position. Aneurysmal bulging area is shown by arrows.

in this region appears definitely weakened and does not contract synchronously with the remainder of the ventricle." His diagnosis at that time confirmed the clinical impression of ventricular aneurysm.

The patient gradually became drowsy and developed marked mental depression; his appetite became poor; his temperature remained about the same. His precordial pain recurred at times and was relieved only by large doses of morphine. By April 16 it had become almost continuous and more severe. His color was ashen, his heart rate was 105, sounds became markedly weakened and the gallop rhythm more pronounced. There was blood tinged expectoration and the lungs showed dullness at both bases posteriorly from the seventh rib to the base on the right side and the eighth rib to the base on the left side, with marked diminution of the breath sounds and râles over these areas and suggestion of a pleural friction rub. Our diagnosis at this time, in addition to the previous diagnosis, was bilateral bronchopneumonia, possible pulmonary embolism, with infarction and bilateral hydrothorax. His condition became rapidly worse and he died on April 13 at 12:30 a.m.

A necropsy, limited to the heart, was performed by Dr. Harold Fink. The heart (figure 10) was found to be somewhat enlarged, weighing 400 gm. There was a distinct aneurysmal bulge of the left border beginning about three cm. above the apex, measuring five cm. in diameter and extending one and a half cm. beyond the margin. The ventricular wall in this aneurysmal portion was markedly thinned out, measuring 0.3 to 0.5 cm. in thickness, while the remainder of the wall was two cm. thick. The inner surface of the aneurysm was devoid of endocardium, being covered by a firmly adherent shaggy membrane. The anterior descending branch of the left coronary artery was completely occluded by an organized thrombus which extended from a point 2.5 cm. below its origin through the remainder of its course. The proximal portion of the vessel showed numerous atheromatous plaques, but no fresh thrombi. The right coronary artery showed similar plaques but was patent throughout its course as was also the circumflex branch of the left coronary artery. However, all

the smaller subdivisions of the left circumflex artery running toward the aneurysm were completely occluded. The right ventricle and the valves showed nothing of significance.

FIG. 10. Gross specimen of the heart showing aneurysmal area (arrows) in its relation to the apex (A). The greater part of the aneurysm has been removed.

Microscopic section showed sclerosis of all smaller arterioles, diffuse brown atrophy of the heart cells and marked diffuse fibrosis. At the site of the aneurysm the endocardium was absent and there was organized blood clot.

The first case is of particular interest because of the patient's age. Although he was only 33 years old at the time of death, and had comparatively little peripheral arteriosclerosis, the coronary system was markedly sclerosed and occluded. Most of the smaller coronary subdivisions appeared like thin threads, as did the main anterior descending branch of the left coronary artery. Such a degree of coronary sclerosis must certainly have taken several years to develop.

In both our cases, acute coronary occlusion of the anterior descending branch of the left coronary artery was the precipitating cause of the aneurysms. Since, in the first patient, the acute occlusion would seem to have occurred only two months before admission, the aneurysm evidently developed within that period. As for the second patient, however, it is difficult to decide to which attack to attribute the aneurysm—the first, 15 years ago, or the second, just preceding admission. If the former, it is difficult to believe a man could live 15 years with a cardiac aneurysm; and if the latter, it is equally incredible that the aneurysm developed within 36 hours, since the bulge was definitely seen on the first roentgen-ray, taken the day after admission.

The pathogenesis of most reported cardiac aneurysms is myocardial infarction secondary to occlusion of a main coronary branch, in an area already the seat of considerable impoverishment of the blood supply. The subjective symptoms are not specific. Evidences of heart failure in various grades and forms, or the anginal syndrome, although present in most reported cases, are merely expressions of coronary and myocardial disease and occur more commonly without aneurysms. Some of the objective findings, however, are important. In the first of our cases the prominence and the diffuse heaving character of the apical impulse, associated with extreme weakness of the first sound over that area, the presystolic gallop rhythm, the localized systolic murmur, together with the weak pulse were sufficient for us to diagnose the condition even in the absence of positive roentgen-ray findings, and were especially significant with the story of recent acute occlusion and the repeated attacks of precordial pain which followed; all of which indicated to us progressive myocardial changes consequent to repeated occlusive processes of the smaller coronary branches. Likewise, in the second case, the prominence of the left border above the apex, the marked diminution of the first sound at the apex (while at the fourth left costosternal junction it was rather intense), the presystolic gallop rhythm, as well as the history, led us to make the diagnosis. The roentgen-ray findings of a bulging area and the fluoroscopic findings of contraction of this area asynchronous with the remainder of the ventricle were sufficient confirmatory evidence.

The recorded cases in the literature that were diagnosed before death showed noteworthy features. In the case reported by Remlinger [14] there was a feeble heart impulse, weak sounds and occasional pericardial friction rub. Lutenbacher [19] stresses the importance of fixation of the apex impulse due to pericardio-diaphragmatic adhesions and tenderness over this area. Harvier and Caroli [17] found in their case two areas of heaving cardiac impulse, one in the sixth space and the other in the fourth with systolic retraction in the fifth space. In McElroy's [23] case there was an expansile pulsating tumor in the apical region extending to the seventh space as far as the anterior axillary line. This was associated with distant heart sounds, a soft feeble murmur, fixation at the apex and a weak pulse. Libman and Sacks [24] and Libman [25] mention a pulsation most marked medial to the apex associated with a dull first sound and gallop rhythm as pathognomonic of aneurysm. To quote Libman "if you get a very poor first sound and if you then get a pulsation more marked between the apex and sternum than at apex, there is practically no condition except aneurysm possible." Christian and Frik [20] diagnosed their case of aneurysm of the upper portion of the left ventricle by an impulse at the left border. Smith [18] diagnosed his by cardiac weakness and persistence of two points of cardiac impulse together with a peculiar outline by roentgen-ray.

If we bear the condition in mind and if we carefully elicit the physical findings, a clinical diagnosis should be made in many cases of cardiac aneu-

rysm especially at the apical region. The roentgen-ray findings are helpful if corroborative; if not and the physical findings point toward the condition, we may consider it at least as a possible diagnosis. The roentgenograms should be made in the antero-posterior and oblique positions and checked up by fluoroscopic examination. Aneurysms above the apex will in many cases then be diagnosed when the physical findings may be doubtful. Aneurysm of the apex, on the other hand, especially of the lower portion, will often escape detection by roentgen-ray as in our first case, but will have definite physical findings pointing toward it. The usual appearance of ventricular aneurysm is a bulging shadow which follows the heart displacements with changes in respiration and position. On fluoroscopic examination there is found a slackening of the movement of the heart at the area of the aneurysm as in the case of Branchi [12] or there is an asynchronous pulsation with expansion, during systole, as in our second case and in the cases of Groedel [11] and Wiberg.[26] The density of the shadow varies with the contents of the aneurysm. If filled with organized clot its shadow is more dense and in the lateral view it stands out as an area of increased density superimposed on the cardiac shadow, as in Branchi's case.[12] Very rarely an organized ventricular aneurysm becomes calcified and will show up as such by roentgen-ray, as was seen by Jaksch-Wartenhorst.[27]

The electrocardiogram offers no specific help in the diagnosis of cardiac aneurysms. In our two cases, as well as in other reported cases, the tracings merely indicate severe myocardial damage. In apical aneurysms, as in our first case, there is a tendency of the major QRS deflections to be directed downward in the second and third leads. This, we believe, is a noteworthy diagnostic sign if taken in conjunction with other evidence. If the pathologic processes in the heart are acute and rapidly developing, we may expect to find the characteristic rapid alterations in the electrocardiographic configurations as in cases without aneurysmal formation.

Summary and Conclusions

Two cases of left ventricular aneurysm, diagnosed during life and proved by autopsy, are reported. One is of particular interest because it occurred in a man of 33 years whose heart was the seat of diffuse coronary sclerosis and occlusive processes with myocardial fibrosis. The findings in these two cases together with some observations reported in the literature lead us to the following conclusions:

1. Most cardiac aneurysms are left ventricular, predominantly in the apical region, and usually follow acute coronary occlusion.

2. The subjective symptoms of cardiac aneurysm are not specific, being merely those of cardiac failure or of the anginal syndrome which may accompany similar cases without aneurysm.

3. The clinical criteria for the diagnosis of ventricular aneurysm are a history of coronary occlusion, an abnormal area of cardiac dullness over

which is heard a very weak first sound, associated with a gallop rhythm usually situated near the left sternal border.

4. The roentgenographic criteria include a bulging shadow following the heart displacements with changes in respiration and position, and slackening of the movements of the heart or asynchronous pulsation, with systolic expansion in that area. If filled with organized clot, an increased area of density will be seen, and calcification, if present, is suggestive.

5. The electrocardiogram is of no specific diagnostic value. Apical aneurysms, however, seem to be associated with major QRS deflections which are directed downward in the second and third leads and in the first lead with a low voltage, upward. This may perhaps be significant as corroborative evidence.

6. Although only about 0.5 per cent of ventricular aneurysms have hitherto been diagnosed during life, we believe that if the condition is borne in mind and attention paid to the above criteria, the diagnosis will be made with increasing frequency.

Addendum

Since submitting this paper for publication, we observed another case of ventricular aneurysm in a 62 year old man, who entered the Coney Island Hospital on July 10, 1934. Four years before admission he had an attack of coronary occlusion and has since been bedridden most of the time. He has had repeated precordial pain which has become worse during the past year. His heart was enlarged especially to the left and presented a distinct apical bulge and a heaving apical impulse on palpation. The sounds were barely audible and no murmurs were ever heard. Blood pressure was systolic 110, diastolic 70 and there was evidence of congestive heart failure. The diagnosis of apical aneurysm was made on the basis of the history, apical bulging and heaving apical impulse associated with a very weak first sound over this bulging area. The diagnosis was confirmed by roentgen-ray which showed " increased prominence of the left upper ventricular border."

He died on September 19, 1934, and at necropsy there was found an enlarged heart weighing 400 gm., with an apical aneurysm four and a half cm. in diameter. There was overlying pericardial exudate, and a complete old occlusion of the anterior descending branch of the left coronary artery.

It is significant that the location of the aneurysm as revealed by postmortem examination did not correspond to the location shown by the roentgen-ray but to the location suspected clinically.

We are indebted to Dr. Philip I. Nash for the privilege of using the material from his Department of Medicine, and to Dr. Michael Gosis for the photographic work used in the illustrations of cases.

REFERENCES

1. Lucke, B., and Rea, M. H.: Studies on aneurysms, Jr. Am. Med. Assoc., 1921, lxxvii, 935.
2. Sternberg, M.: Das chronische partielle Herzaneurysma, 1914, F. Deuticke, Leipzig and Vienna.

3. HALL, D. G.: Cardiac aneurysms, Edinburgh Med. Jr., 1903, xix, 322–346.
4. WILSON, C. P.: Mycotic aneurysm involving the intraventricular septum, Am. Heart Jr., 1926, i, 703–706.
5. PREBLE, R.: Discussion of the paper of MCELROY, J. B.: Jr. Am. Med. Assoc., 1908, li, 375.
6. JOACHIM, H., and MAYS, A. T.: Case of aneurysm probably of traumatic origin, Am. Heart Jr., 1927, ii, 682–686.
7. PLETNEW, D. D.: Lässt Sich ein Aneurysma der Herzventrikel intra vitam festsellen? Ztschr. f. klin. Med., 1926, civ, 378–393.
8. STEEL, D.: Roentgen diagnosis of cardiac aneurysms, Jr. Am. Med. Assoc., 1934, cii, 432–436.
9. LENK, R.: Röntgendiagnose der Koronarsklerose in vivo. Gleichzeitig ein Beitrag zur Erkennbarkeit des Herzaneurysmas in Röntgenbilde, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1927, xxxv, 1265–1268.
10. ALBRECHT, H. U.: Röntgenologisch diagnostiziertes und autoptisch bestätigtes Herzaneurysma, Zentralbl. f. inn. Med., 1932, liii, 557–562.
11. GROEDEL, F. M.: Der röntgenologische Nachweis des Herzaneurysmas, München. med. Wchnschr., 1933, lxxx, 210–211.
12. BRANCHI, H.: Aneurysm apparently due to trauma, La Ligura Medica, 1922, 12.
13. FOGEL, E. I.: Aneurysm of the left ventricle following coronary infarct in living patient, Jr. Am. Med. Assoc., 1933, c, 39–41.
14. REMLINGER, P.: Sclérose de l'artère coronaire intérieure; dégénérescence consécutive du ventricule gauche; anévrysme du coeur diagnostiqué pendant la vie, Bull. méd., 1896, x, 483–485.
15. VOELCKER, A. F.: Trans. Path. Soc., London, 1902, 53.
16. QUERALTO, J. G.: Aneurisma Ventricular Izquierdo, Estudio Clinico y Anatomopathologico, Mundo Medico, 1932, xiv, 1158.
17. HARVIER, P., and CAROLI, J.: Sur un cas d'anévrysme de la pointe du coeur, Paris méd., 1930, ii, 30–36.
18. SMITH, E. S.: Aneurysm of heart complicated with chronic mediastinopericarditis, Southern Med. Jr., 1922, xv, 962–971.
19. LUTENBACHER, R.: Anévrismes du ventricule gauche, Arch. d. Mal. du coeur, 1920, xiii, 49–58.
20. CHRISTIAN, and FRIK: Rontgenbefundbei chronischen partiellen Herzaneurysma, Klin. Wchnschr., 1932, i, 582.
21. HUGHES, F. M.: Rupture of the heart due to aneurysm of the myocardium, Lancet, 1914, i, 533.
22. WILSON, C.: Aneurysm of the heart without symptoms, Lancet, 1919, ii, 199.
23. MCELROY, J. B.: Aneurysm of the heart with report of a case associated with mediastinopericarditis, Jr. Am. Med. Assoc., 1908, li, 371–374.
24. LIBMAN, E., and SACKS, B.: A case illustrating the leukocytosis of progressive myocardial necrosis following coronary artery thrombosis, Am. Heart Jr., 1927, ii, 321–326.
25. LIBMAN, E.: Methods of physical examination with special reference to painful disease of the thorax and abdomen, Interstate Postgrad. Med. Assoc. of N. Am., Cleveland Proc., October 1926, p. 60.
26. WIBERG, G.: A case of aneurysm of the heart, Acta radiol., 1931, xii, 562–573.
27. JAKSCH-WARTENHORST, R.: Beitrag zur Klinik der Herzventrikelaneurysmen, Deutsch. Arch. f. klin. Med., 1928, clix, 197–203.

VASCULAR CRISES*

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ALMOST before we were aware of it, a striking innovation appeared in medical nosography and medical practice. A new specialty has developed which was hardly dreamed of three or four years ago—a specialty dealing with diseases of the blood vessels.

In our textbooks the subject of these diseases, particularly insofar as it concerns the arteries, is dealt with largely as static—uninterestingly and briefly. But within an unbelievably short space of time, disease of the blood vessels has become a dynamic, active branch of medicine with a rapidly growing literature of its own. Some may decry such intensive specialization in medicine, but it cannot be denied that concentration upon one field broadens our knowledge, though it may narrow the broadeners. The new specialty, which might be called angiology, has already a large number of devotees in this country and abroad, and is bringing under its aegis diseases that previously did not seem to have any connection with it. In a number of hospitals special vascular clinics have been created and the men in these clinics are taking their place beside the cardiologists and the allergists.

When we look into the history of the subject we find, as in nearly every other phase or department of medicine or science, that its roots go far back and that we are by no means the pioneers that we may fondly think ourselves. As is pointed out so wonderfully in Thomas Mann's "Joseph and His Brothers," when we come to what seems the beginning of anything in history, it is not the beginning though want of knowledge may make it seem so. Therefore when I start in 1773 with Stephen Hales' "Haemodynamics," it is in implied recognition of Mann's thesis. Hales was seemingly the first to advance the notion that the arteries were contractile. With plain water he perfused an aorta and its mesenteric vessels at a constant pressure head and noted the outflow to be greater when the fluid was warm. Investigating also the effect of alcohol and extract of cinchona bark, he was led to conclude that some drugs caused constriction and some dilatation.

E. H. Weber appears to have been the first to assume a nervous control of contraction, advancing the hypothesis to explain blanching and pallor on one side and blushing on the other.† Perhaps before Weber I ought to mention Allan Burns, who in 1809 explained angina pectoris on the basis of a spasmodic contraction of the coronary arteries—a very ingenious and fertile thought. The muscular coat of the arteries was not described until 1840, when Jacob Henle reported its existence, and then Claude Bernard in

* Read at the Meeting of the Interstate Graduate Assembly at Philadelphia, November 6, 1934.

† Thomas Willis (1621–1675) had a working hypothesis of the vasomotor nerves. "These small lines and cords of nerves do variously straighten, compress, or it may be sometimes quite shut these blood-carrying vessels" by acting on the muscular coat of the vessels to which they are distributed.[1]

1851 noted the effect of cutting the sympathetic nerve on the vessels of the rabbit's ear and the effect of stimulation of the nerve. With these cumulative observations, the relation of the sympathetic nervous system to the caliber of the blood vessels became firmly established.

The earliest clinical observation—I use the superlative with the reservation mentioned above—is probably that of Charcot in 1858 on Intermittent Claudication,[2] a condition described as occurring in horses by Boulay in 1831. Four years after Charcot's publication, there appeared what is still the most important essay in the entire field of vascular diseases, namely Raynaud's classical thesis "On Local Asphyxia and Symmetrical Gangrene of the Extremities."[3] Goltz in 1874 suggested the existence of a vasomotor mechanism in the peripheral vessels, in the ganglion cells of vasomotor nerves.

The next milestone is represented by Pal's epochmaking monograph on Vascular Crises.[4] After the lapse of a dozen years, Buerger's[5] masterly article on Thromboangiitis Obliterans appeared and marks another milestone. Since then the literature has grown so fast that it is impossible to do it justice. I shall mention only a few outstanding contributions: Krogh's pioneer work on the capillaries, that of Lériche, the father of sympathectomy, that of Cannon on the sympathetic nervous system and the endocrine glands, that of Sir Thomas Lewis and his associates on the capillaries, that of Brown, Adson and other members of the Mayo Clinic, on various phases of vascular disease, the work of Lichtwitz, Alice Bernheim, Starr, Landis, Scott, Kramer, Herrmann, Bastai and Dogliotti, and many others.

The vasomotor nervous system which has its centers in the medulla and in the spinal cord, is distributed chiefly to the arterioles and capillaries but also to the veins and large arteries. The nervous apparatus in the vessel walls regulates the tonus of the vessels. This tonus, which together with the force of the heart maintains the blood pressure, is very sensitive and is readily influenced by many factors such as hormones, temperature, emotions and sensations, activity of the muscles or of the internal organs, poisons, etc. While the tonus influences the blood pressure, the corollary is also true that the state of the blood pressure reacts upon the sympathetic nervous system and thereby affects the tonus of the vessels. Although the vascular tonus is directly under the influence of the sympathetic nervous system, the latter in turn is brought into action or inhibited, as the case may be, by hormones of various ductless glands—the adrenals, pituitary, parathyroids, sex glands, and thyroid. The study of the interrelation of these glands, a factor in what Cannon calls homeostasis, constitutes one of the most difficult and important biological problems.

The vasomotor nerve impulses seem to reach the vessels along their whole length and not only in a single trunk at the beginning. This is important in connection with sympathectomy—cutting the perivascular nerves of any one segment does not wholly deprive the vessels of their vasoconstrictor innervation. The predominant vasomotor impulses are constrictor in nature;

dilatation of the blood vessels has by some been looked upon as a passive process resulting from inhibition of the vasoconstrictor mechanism, but there is considerable experimental proof that dilatation itself may at times be active. In animals dilatation can be produced by stimulating the central end of the depressor nerve after all vasoconstrictor fibers have been severed. Such a result would imply the existence of a vasoconstrictor center but this conclusion cannot be applied to man without some corroborative observations that are still lacking.

At its bifurcation the carotid artery is somewhat enlarged—the carotid bulb or sinus—and is here surrounded by a plexus of nerves. Pressure upon the sinus causes slowing of the heart and lowering of blood pressure. (Czermak's phenomenon.) At first it was believed that the effect was due to direct pressure on the vagus nerve, but Hering, Hymans and others have shown that the effect is due to a reflex stimulation of vagus inhibitory fibers through pressure on the carotid sinus nerves. Very little is known of the share of the carotid sinus in the vascular tonus in man, whether it is constrictor or dilator, or actually, whether it plays any rôle whatever.

The vasomotor system, including in this the intrinsic and extrinsic mechanisms, is very sensitive. This sensitiveness is well shown in a simple experiment devised by Landis and Gibbon.[6] When the hands and forearms are immersed in warm water, a decided rise in surface temperature occurs in the cool lower extremities within 15 minutes—from 26° C. (78.8° F.) to 32° C. (89.6° F.). The reflex effects of cold, acting through the medium of the vasomotor system, are demonstrated in the experiments of Hines and Brown.[7, 8] By putting one hand in ice water for 20 to 30 seconds, an immediate rise in both systolic and diastolic pressure is produced. The response is not augmented by placing both hands or both feet or all four extremities in ice water. It is interesting and for future studies very significant that persons with established essential hypertension and even those in what might be called the functional or preclinical stage of hypertension give an exaggerated response, showing an increased vasomotor irritability.

In a virtually new and not yet overclassified subject such as diseases of the blood vessels a variety of classifications is possible. From a clinical point of view we shall find it advantageous to speak first of all of general and of local vascular crises, which may again be subdivided into constrictor and dilatational crises.

1. *General Constrictor Crises.* These are exemplified by the sudden rises of blood pressure that occur both in apparently healthy and in hypertensive individuals. Among the former it is the lively, excitable, intense type that is subject to sudden rises of blood pressure. These crises are of brief duration and usually pass off without any deleterious effects. It is possible, however, when these crises are oft repeated, especially under the influence of psychic stimulation, as pointed out by Schreiber, that they eventually lead to a permanently heightened tonus, to hypertrophy of the muscular coat of the arterioles, and to hypertension.

In the hypertensive group—and it should be remembered that the blood pressure need not be extremely high—sudden vascular crises may produce a variety of nervous symptoms: headache, vertigo, tinnitus, aphasia, monoplegia, hemiplegia, hemianopsia, convulsions. It may not always be easy to decide whether these symptoms are due directly to a general hypertensive crisis or to localized functional or anatomic changes that precede and cause the rise in blood pressure.

The relation of general hypertensive crises to angina pectoris has recently been studied by Sir Thomas Lewis.

General vascular crises are common in women at the time of the menopause—which makes it highly probable that some endocrine imbalance resulting from atrophy of the ovaries or changes in related glands plays an etiologic rôle.

General dilator crises manifest themselves in a sudden fall of blood pressure. In practice it may be difficult to decide how much of the fall is due to vascular dilation—whether from constrictor paralysis or dilator stimulation—and how much to cardiac weakness. In the collapse of acute infectious diseases and in traumatic shock vasomotor paralysis is the predominant mechanism, although in the former some element of heart weakness is added. A preliminary vasomotor spasm of the surface usually attends shock. In sudden coronary obstruction, in acute cardiac dilatation, in rupture of the heart, there is a tremendous fall of blood pressure from direct depression of the cardiac function. The symptoms of dilator crises resemble those of severe hemorrhage—profound weakness, pallor, sweating, sighing respiration, dizziness, thready pulse, at times unconsciousness. Dilator crises are produced as already indicated, by acute infections, by shock, traumatic and surgical—toxic agents such as histamine may here play a part—at times by changes in posture (postural hypotension), and by Addison's disease.

2. *Local Vascular Crises.* These are chiefly of the constrictor type, but blushing and other forms of erythema, even the redness of inflammation are examples of local dilatation. While local vascular crises or angiospasms are usually brought about by stimulation of the nervous vasoconstrictor mechanism, a myogenic contraction excited by hormones or other agents is conceivable. Just as we have in the heart a myogenic contraction but one profoundly influenced by nerve impulses, so we may assume a similar mechanism in the arterioles, the muscular coat of which is large in proportion to lumen. Certain individuals, according to Lichtwitz,[9] suffer from an angiospastic diathesis. They are in consequence subject to angiospasms in various parts of the body, particularly in the veins of the liver and spleen. Spastic closure of these prevents an adequate amount of blood from getting out of the natural reservoirs which in turn leads to anemia or ischemia elsewhere.

The results of spastic contraction as well as of any other form of vascular occlusion depend upon a variety of factors: the size of the occluded

vessel, the duration of the spasm, the previous state of nutrition of the part, and the possibilities of prompt and adequate collateral circulation. I once saw the pulse suddenly disappear completely at the wrist through spasm of the radial artery without any observable after-effects. In some organs there is so little anastomosis between the vessels of contiguous territories (end arteries) that even a brief obstruction produces functional and usually also structural changes. Diseased vessels, unless they have entirely lost their contractile power, are more sensitive to vasomotor influences than normal vessels but, while more responsive, they return more slowly to their previous state. Under some conditions vessels, the coats of which are anatomically entirely normal, show a vasomotor hypersensitiveness. Such conditions occur in certain constitutions, often on a racial basis, and in individuals of peculiar psychic and physical makeup.

It has usually been held that the functional effects of cutting off the blood supply to a territory depend upon the lack of nutritive material, but it is highly probable that it is principally the local deprivation of oxygen that is responsible for the primary results of vascular obstruction.*

The subject of local vascular crises is rendered somewhat difficult by the fact that in some territories identical functional results are produced by angiospasm, by embolism, and by thrombosis. This is particularly true of the brain. What I have to say about the symptoms of cerebral angiospasm may therefore be applied in large measure also to those other forms of obstruction.

Cerebral Angiospasm. On account of the complexity of the cerebral functions, angiospasm produces a multiplicity of symptoms which have one feature in common—they are as a rule of short duration. They occur most frequently in hypertensive individuals, but also in persons whose pressure is not markedly abnormal. According to location, we may have monoplegia, hemiplegia, aphasia, hemianopsia and other visual defects, convulsions, and possibly also psychomotor and psychic disturbances. There is a good deal of evidence that migraine is dependent upon angiospasm, perhaps allergic in ultimate origin.

I have just said that convulsions may be due to angiospastic states. The type of seizure I have in mind occurs most often in persons of middle or late life who have suffered long from hypertension; not exclusively, however, for I have seen them in individuals with blood pressures but little above the normal.

Those unfamiliar with the convulsions in question are apt to diagnose them as genuinely epileptic or as uremic, the latter especially because a little albumin is usually found in the first urine passed after the fit. If one studies the history of these patients, one finds that the convulsions had no connection with childhood and adolescence, that the first seizure occurred in the sixth or seventh decade, and that they repeated themselves at irregular

*For the local deprivation of oxygen to the tissue I have proposed the word histanoxia (from ἱστος, tissue, ἀνοξία, without oxygen). The term anoxemia sometimes used for oxygen starvation connotes rather a general state of the blood than a local condition.

intervals. As a rule, the convulsions leave no aftermath; occasionally some disturbance of speech, of vision, or of mentality persists for a while. If the patient is seen just before or during an attack his blood pressure, both systolic and diastolic, will be found raised considerably above its habitual level. To distinguish this epileptiform convulsion from true epilepsy, it has been called epilepsia tarda or senile epilepsy.[10]

The best treatment for the attack is bleeding from the arm; preventive treatment involves the general measures applicable to hypertension as well as those made use of in true epilepsy.

Uremia and eclampsia are very similar to epilepsia tarda and may also represent vascular crises. In the diagnosis the convulsions of general paralysis of the insane must also be borne in mind. When they are the inaugural symptom, they may, as I have seen, give rise to much perplexity until a positive Wassermann test is obtained with the spinal fluid.

A variety of transient sensory and psychic disturbances may have an angiospastic origin—vertigo, tinnitus aurium, hemianopsia, quadrant anopsia, disorders of color vision, amaurosis, and headache. Migraine or hemicrania, as already mentioned, is perhaps an angiospasm on an allergic basis. Spasm of the homolateral temporal artery has been observed during the migrainous attack. Among psychomotor and psychic phenomena producible by angiospastic states, sensory aphasia, amnesia and brief psychotic outbursts may be mentioned.

Vascular Crises in the Eye. Aside from intracerebral conditions, local vascular crises may produce disturbances of vision. These local crises are traceable to spasm and embolism of the central artery of the retina.

Vascular Crises in the Ear. It is possible that angiospasm may play a rôle in some forms of sudden tinnitus and vertigo, but little is known about it. It is a subject in which the coöperation of otologists is necessary for a better understanding.

Vascular Crises in the Lungs. We know comparatively little about these in man; in animals they can be induced by anaphylactic shock. There is, however, a condition in the human subject that has the hall-mark of a vascular crisis, although its true pathogenesis, its morbid physiology, are but imperfectly understood. I refer to acute or fulminant pulmonary edema. Its chief clinical cause is myocardial disease usually associated with hypertension. It is also met with in mitral stenosis and after the removal of pleural fluid by tapping. Acute pulmonary edema, which has a striking tendency to recur, puts the patient's life in great peril—he may drown in his own juices. While the attack endures, dyspnea, air hunger and cyanosis are very marked and the chest, back and front, is full of moist râles. The patient often but not invariably expectorates quantities of clear or faintly blood-tinged sputum which coagulates on boiling.

Treatment promptly instituted usually brings about speedy recovery. The best measures are a hypodermic injection of morphine sulphate, gr. 1/4,

and atropine sulphate, gr. 1/150; venesection and dry cupping over the chest.*

Whether there is a vascular as well as a bronchial spasm in asthma is as yet undetermined.

Vascular Crises in the Heart. From the clinical as well as from the scientific point of view, this is one of the most important phases of my subject. The whole matter culminates in the question—what is the relation of coronary spasm to angina pectoris? Personally I believe it is that of cause and effect. While other causes may be operative, perhaps in the end they act as angiospastic factors or agents. Lichtwitz [9] believes that besides coronary spasm, angina pectoris may be produced by the failure of the physiologic dilatation during increased activity, and by the nonappearance of the increase of the circulating blood during work and under conditions of low temperature. This last circumstance may be brought about by pathologic closure of the veins of the liver and spleen whereby the blood reserve of these great reservoir organs instead of being added to the circulation is retained. This little understood mechanism, angiospastic in character, in itself does not eliminate the possibility of coronary spasm.

Vascular Crises in the Abdomen. Angiospasm analogous to that supposedly at the basis of angina pectoris may occur in the abdominal vessels (angina abdominis). I have seen this in a case reported elsewhere.

Some writers attribute the gastric crises of locomotor ataxia and the colic of lead poisoning to angiospasm, a view that has much in its favor, although it may not be the whole explanation,—it hardly accounts for the obstinate constipation of lead poisoning or for the persistent, uncontrollable vomiting of tabetic crises.

Vascular Crises in the Skin. Blushing and pallor of the face are vascular crises. The causes are manifold, but emotional factors seem most important.

Another dermal vascular crisis is urticaria or hives. This is a capillary crisis brought about, it is believed, by the liberation through toxic or toxicotraumatic action (bee sting, wasp sting, etc.) of histamine-like substances which act upon the smaller vessels and capillaries in such a way that fluid exudes into the perivascular tissues. Angioneurotic edema is of the same nature as urticaria. For reasons at present beyond our ken, urticaria is attended by intense itching, angioneurotic edema is not. Dermographia also belongs to the same category of skin conditions.

Vascular Crises in the Extremities. It is in this special field that the subject of vascular diseases has in a short space of time won its greatest triumphs. The progress, it must be admitted, has accrued more to the advantage of diagnosis than to that of treatment, but better diagnosis is bound

* Dry cupping is best done by taking a half dozen smooth wine or whiskey glasses, moistening the inside with grain alcohol, lighting the alcohol with a match and slapping the glass on the chest, either front or back, while the alcohol is still burning. Six or eight of such cups may be applied in a few minutes. When the raised skin inside the cup begins to look purple, the cup is removed. The procedure has virtue although we do not know its modus operandi.

to lead eventually to better treatment. The objectives of study have been in general the following:

1. The causes of vascular disease of the extremities.
2. The extent of the disease, i.e., how far down or high up it has reached; also the type of vessel or vessels involved.
3. The character of the disease, whether spastic, i.e., functional, or organic.
4. Treatment, which is subdivisible into:
   - (*a*) Cure or palliation.
   - (*b*) Arrest of the process.
   - (*c*) Prevention of gangrene.
   - (*d*) Treatment of gangrene.

Causes of Vascular Disease of the Extremities. Under this head I shall consider the principal clinical entities or syndromes in which vascular disturbances play the leading rôle.

One of the earliest to attract attention was intermittent claudication, the symptoms of which are quite uniform. The patient after walking a short distance is seized with a painful cramp in the calves that compels him to stop walking. After a brief rest, from a few seconds to 10 minutes, he can proceed with ease. The amount of exercise causing the cramp, as Goldsmith and Brown [11] have shown, is remarkably constant. One of my patients experienced the cramp only on the street; he could walk about his factory all day unhindered. A large proportion of sufferers have flat feet; many are heavy smokers; nearly 50 per cent of those affected are Jews of eastern origin, and, of course, the male sex preponderates greatly. Examination usually shows thin, cold feet with absence of pulsation in the dorsalis pedis and posterior tibial arteries; the roentgen-ray may reveal more or less extensive calcification of the vessels.

The pain in intermittent claudication is the result of a temporarily inadequate blood supply to the working muscles, but whether it is due directly to ischemia, to histanoxia, or to certain changes in the muscles has not been definitely determined. The production of vasodilatation by the means now employed does not seem to have much effect on the disease, and certain tissue extracts that exert a favorable influence upon it do not seem to do so by vasodilatation.

Intermittent claudication is a precursor (75 per cent) or accompaniment (98 per cent) of that terrible disease, thromboangiitis obliterans. As a primary disease, it occurs in later life than thromboangiitis obliterans and is associated with or is dependent upon arteriosclerosis. In thromboangiitis, calcification of the blood vessels is rare, the process being a diffuse inflammation with thrombosis of arteries and veins. In the primary form of intermittent claudication complete recovery is possible under proper treatment; the more spasm and the less sclerosis, the better the prognosis.

False diagnoses are often made—rheumatism, metatarsalgia, flat feet, sciatica. As regards sciatica, one should bear in mind that "bilateral

sciatica" is almost never sciatica. It may be intermittent claudication, diabetic or nephritic neuritis, cord tumor or pelvic pressure. Perhaps the most important point to bear in mind is that intermittent claudication may be an inaugural symptom of Buerger's disease.

Thromboangiitis obliterans should perhaps be excluded from consideration here as it is not a vascular crisis, a functional condition, but an organic disease. However, it deserves inclusion for there is in addition to the marked structural changes a tendency to angiospasm. Naturally this is most marked in the early stages of the disease. Thromboangiitis, so well described by Buerger, was at one time believed to occur almost exclusively in Russian Jews, but the great experience of the Mayo Clinic has shown that this undesirable prerogative no longer belongs to that racial group. Only one-half the thromboangiitis patients seen in that clinic are Jews; the others represent all races including native American stock. It has not been observed in full-blood negroes.[12] The disease occurs in men between the ages of 25 and 50 years; in the Mayo Clinic there were only six patients aged more than 60 years in a series of more than 500 cases.[13]

The cause of thromboangiitis is unknown. The nature of the process suggests an infective agent but beyond that and a limited number of experiments, such as successful transplantation of resected veins the seat of phlebitis, there is no definite evidence. A second hypothesis ascribes the disease to excessive cigarette smoking. It is true that, as Barker[14] has shown, the majority of patients, 91.5 per cent, who had thromboangiitis obliterans used cigarettes. On the other hand, Brown[12] has observed the disease in a group of patients who never used tobacco in any form. There is no doubt, however, according to the researches of Maddock and Coller[15] and of Barker[14] that the smoking of cigarettes exerts a vasoconstrictor effect, and Harkavy, Hebald and Silbert[16] and Sulzberger[17] have demonstrated a marked skin hypersensitiveness to tobacco in patients suffering from Buerger's disease.

I shall not describe the symptomatology of the disease in its entirety, as in this article I am concerning myself chiefly with vascular crises. Angiospastic phenomena are common in thromboangiitis; they result from sensory vasomotor reflexes and cause blanching and cyanosis, and a numb, dull, aching sensation on exposure to warmth. The frequency of these spastic disturbances has been the cause, as pointed out by Brown, of errors in diagnosis—Raynaud's disease being diagnosed in male patients, despite the fact that most of the patients who have Raynaud's disease belong to the female sex.

Before describing the methods of determining the vasospastic element and the location of the lesion, I shall discuss the subject of Raynaud's disease inasmuch as the same procedures are employed for its study. In fact, these procedures are now used in the investigation of all peripheral vascular disturbances, including diabetic and arteriosclerotic gangrene, embolic obstruction, and other affections hereafter to be mentioned.

Raynaud's disease has undergone hardly any changes since it was first described in 1862 by Maurice Raynaud, the man whose name it bears. The disease is a bilateral, symmetrical affection, occurring almost exclusively in women (men 5 per cent) and is characterized by intermittent attacks of changes in color, from pallid or dead-white to deep purple or black, and by trophic changes ending at times in gangrene. Additionally characteristic is the absence of occlusive lesions in the peripheral arteries. Very little is known of the etiology of Raynaud's disease. That the endocrine glands, particularly the ovaries, play a rôle, might be inferred from the preponderance of the female sex. Bernheim and Garlock (personal communication) believe that there is a disturbance in the calcium metabolism for which the parathyroids may be responsible. They have seemingly cured a number of cases by parathyroidectomy.

Scleroderma begins as an angiospastic condition; it may be preceded or accompanied by typical Raynaud's phenomena. But a mere angiospasm hardly accounts for the profound changes in the skin and subcutaneous tissues—with atrophy, adhesion and contraction of the integument—not only in the extremities but in the face, especially about the mouth, over chest and clavicles, indeed over any and all parts of the body. In a doctor's wife now under my care there is hardly an area that is not hide-bound. Severe trophic changes have occurred at the finger tips, over the digital joints, elbows and knees, and about the mouth. It is difficult to decide whether the primary process is a spastic occlusion of the vessels or whether the trophic changes, atrophy and tightening of the skin, squeeze the blood out secondarily.

Acrocyanosis is an obscure condition which affects the hands and feet, producing a bluish or reddish color and coldness. The affection is very annoying. I have seen it in two sisters, saleswomen, who were embarrassed as customers would comment on the appearance of their hands. It is most marked in cold weather but in some persons it persists even in warm weather. While resembling the asphyxial stage of Raynaud's disease, it cannot be classed with that condition as it is more permanent, especially in cold weather, and is without pain and without trophic changes. It would appear to be due to an angiospasm that reduces the capillary flow through the skin.

Erythromelalgia, a vascular disorder first described by Mitchell,[18] represents a vasodilator rather than a vasoconstrictor type of disease. It has the following features: attacks of pain and burning in the extremities, with throbbing and pulsation in the arteries and arterioles and usually with redness from dilatation of the surface capillaries and venules. The condition is bilateral and is intensified by heat and by exercise, and is relieved by rest, cold and elevation. As thus defined it constitutes a clinical entity, although its cause is unknown. Symptoms resembling erythromelalgia may be met with in other diseases, in thromboangiitis obliterans, in polycythemia rubra, but under such conditions it does not constitute the real disease.

The Cause of Pain in Angiospasm. Perhaps the question should be put in another form: why is the stopping of the blood supply to a part painful? The answer is difficult; the cause of the pain may not always or everywhere be the same. Sir Thomas Lewis explains the pain in intermittent claudication on the basis of an accumulation of metabolites in the muscles. This view is to some extent corroborated by the result obtained with injections of pancreatic tissue extract * in muscle pain of ischemic origin.[19] It was found that pain was relieved even though no dilatation of the vessels took place. There are, however, circumstances in which the metabolite theory would seem to be inadequate. A sudden blocking of a vein may be accompanied by violent pain as if the part had been struck. It is difficult to see how metabolites can be formed so promptly. The pain that follows the sudden closure of an artery has been attributed to a stretching of the artery proximal to the seat of closure. This would postulate a pain comparable with biliary and ureteral colic.

One of my patients suffering from polycythemia rubra was one day seized with violent pain in the left testicle. I found what seemed to be a thrombosis of the veins. Subsequently he had a similar attack about the ankle. In the case of the testicle the formation of metabolites is not likely to play an important rôle.

The conclusion seems warranted that the causes of pain in vascular occlusion, whether spastic or obturative, are multiple:

1. The accumulation of toxic metabolites in active tissues, especially muscles.

2. Histanoxia, ischemia or local anoxemia.

3. Pressure upon sensory nerve endings in the walls of vessels either through stretching proximal to the obstruction or through an actual squeezing of the nerve endings during spastic contraction. In either case, there would also be an inadequate blood supply to the vessel itself and to the surrounding receptor organs.

We may now take up the newer methods of determining the seat of obstruction and the presence or absence of angiospasm as an element in the ischemic process. In discussing these methods I shall borrow considerably from articles by Brown,[8] Kramer,[20] Starr,[21] Scott and Morton,[22] Pearse and Morton,[23] and others.

1. *Inspection and palpation* give information of great value. Coldness up to a certain point indicates how far the circulation, direct and collateral, is inadequate. Absence of pulse in the dorsalis pedis artery is an important finding in most cases of intermittent claudication and advanced arteriosclerosis. Such absence is not infrequent in cases of coronary sclerosis.

2. *Measurement of surface temperature,* by means of delicate instruments. This is particularly useful when one wants to differentiate between angiospasm and mechanical occlusion. Readings are taken before and after nerve block. The pressor or vasoconstrictor impulses may be blocked either

* The active substance in the extracts may be adenylic acid or adenosin.

by spinal or general anesthesia or by local infiltration of the nerves to the part to be studied, or inhibited by artificial fever induced by intravenous injection of a foreign protein, e.g. typhoid vaccine. The block is normally followed by a rise of several degrees in the surface temperature, such rise being an indication that the spasm has been overcome. If there is no rise, then the obstruction of the blood vessels is not spastic but organic. Tests for the vasospastic element are of special importance in cases in which surgery is contemplated—sympathectomy, ganglionectomy or ramisectomy. If the surface temperature does not rise adequately, little can be expected from these operations.

The surface temperature of the lower extremities may also be raised reflexly by immersing the forearms and hands in warm water.[6] Landis and Gibbon found that if the forearms are immersed for 35 minutes in water at a temperature of from 43 to 45° C., a vasodilatation is produced in the lower extremities. If the surface temperature rises to above 31.5° C. significant structural disease of the arteries of the lower extremity is definitely absent. If the surface temperature fails to rise to this level, organic arterial obstruction is probably present.

3. *Oscillometry.* The oscillometer determines the magnitude of pulsation of the arteries and is helpful in determining in the case of organic obstruction the point to which the circulation is adequate.

4. *Calorimetry.* By determining the amount of heat loss in a given time and by skin temperature observations, calorimetric methods give indirect information of the volume flow of blood through an extremity.

5. *Histamine Test.* When a minute amount of histamine is introduced into the skin a reaction occurs which Sir Thomas Lewis [24] and Lewis and Grant,[25] have classified as (1) local dilatation, (2) flare, or (3) wheal. Starr [26] has employed this reaction as a test for circulatory deficiency in the feet. In cases in which the circulation to the feet is impaired, the reaction to histamine is delayed, reduced or incomplete.

6. *The Roentgen-Ray.* This will show calcification of the arteries if it is present, but calcification may exist with good circulation.

Visualization of the arteries by means of the injection of opaque solutions has been tried by a number of investigators.[27, 28] Allen and Camp, using a preparation of thorium dioxide called thorotrast, were able to demonstrate by means of arteriography, thromboangiitis obliterans in two cases in which all other methods of examination had given inconclusive information. The attitude of the profession toward the introduction of radioactive substances into the body is distinctly one of fear. The method as employed by Allen and Camp, excellent as it is in its immediate results, will not become widely used until more is known of the effects of the prolonged presence of thorium in the body.

Treatment. The vasomotor crises in the extremities, characterized as they nearly always are by pain, must be treated both causally and symptomatically. I need not discuss the causal treatment in such cases as are due

to diabetes mellitus and shall limit myself to those measures that improve or restore the circulation when it is cut off or greatly reduced through arteriospasm.

To improve the peripheral circulation in vessels the seat of constrictor spasm several means are at our disposal.

1. Alternate elevation and lowering of the limb. This exercise is capable of producing a better inflow and outflow of blood. It is applicable to practically all cases of obscure pains in which the cause is a local ischemia.

2. Alternate applications of heat and cold.

3. The use of dry heat applied by means of electric bulbs. Great care must be exercised in not exposing the parts to too much heat.

4. Alternate suction and compression in an air-tight chamber, a method, suggested by Herrmann and Reid.[29] It is too early to speak of its value in angiospastic conditions in the limbs. The limb is placed in a glass chamber and by means of a special motor air is alternately sucked out and forced in. Herrmann's apparatus, called Pavaex (from Passive Vascular Exercise) and the device of Landis work on slightly different principles, but have the same underlying objectives.

5. The injection of sodium chloride solution. This is most useful in thromboangiitis obliterans; it probably acts less by relieving spasms than by altering the state of the blood.

6. The administration of calcium has been found useful in Raynaud's disease and allied conditions. The dose must be fairly large, from 1/2 to 1 gram of calcium gluconate twice daily. The calcium should be given an hour before meals.

7. Acetyl beta-methylcholine chloride, commercially known as mecholine or mecholyl, has experimentally and clinically been found to cause vasodilatation. Its administration is made a little difficult by the fact that it is exceedingly deliquescent. The dose by mouth is 0.2 to 0.5 gram, three times a day; best dissolved in a little water and then mixed with milk. It may also be given subcutaneously—never intravenously—in doses of 5 to 10 mg., to be increased up to 25 mg. according to the patient's tolerance. Recently Kovacs [30] and Doane [31] administered it by the method of iontophoresis, which introduces the substance electrically into the limb.

In some cases, especially in acrocyanosis, endocrine preparations may be useful. Theelin has been tried.

8. Parathyroidectomy in the treatment of Raynaud's disease has given encouraging results but further observations are necessary before a final judgment can be reached.

I shall not go into details of the surgical operations that have been recommended for angiospastic conditions but merely mention them—sympathectomy, ganglionectomy, ramisectomy. The usefulness of these procedures is very limited and in the case of sympathectomy the results are rarely permanent.

BIBLIOGRAPHY

1. Miller, W. S.: Thomas Willis (1621–1675), Bull. Soc. Med. History of Chicago, 1923–1925, iii, 215–232.
2. Charcot: Compt. rend. Soc. biol., 1858, xii, 225.
3. Raynaud: De l'asphyxie locale et de la gangrene symmetrique des extremites, Thesis, Rignoux, Paris, 1862.
4. Pal: Gefässkrisen, 1905, S. Hirzel, Leipzig.
5. Buerger: Thromboangiitis obliterans, Am. Jr. Med. Sci., 1917, cliv, 319.
6. Landis, E. M., and Gibbon, J. H., Jr.: Simple method of producing vasodilatation in lower extremities, with reference to its usefulness in studies of peripheral vascular disease, Arch. Int. Med., 1933, lii, 785–808.

   Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in lower extremities in response to immersing forearms in warm water, Jr. Clin. Invest., 1932, ii, 1019–1036.
7. Hines, E. A., Jr., and Brown, G. E.: Standard stimulus for measuring vasomotor reactions: its application in study of hypertension, Proc. Staff Meet., Mayo Clin., 1932, vii, 332–335.
8. Brown, G. E.: Functional or preclinical stage of essential hypertension, Jr. Tenn. Med. Assoc., 1933, xxvi, 321–325.
9. Lichtwitz, L.: Angiospastic diathesis, Med. Clin. N. Am., 1934, xvii, 1407–1415.
10. Riesman, D., and Fitz-Hugh, T., Jr.: Epilepsia tarda, Ann. Int. Med., 1927, i, 273–282.
11. Goldsmith, G. A., and Brown, G. E.: Pain in thromboangiitis obliterans, Proc. Staff Meet., Mayo Clin., 1934, ix, 201–202.
12. Brown, G. E.: Thromboangiitis obliterans; Buerger's disease, Surg., Gynec. and Obst., 1934, lviii, 297–311.
13. Horton, B. T., and Brown, G. E.: Thromboangiitis obliterans among persons past middle age, Ann. Int. Med., 1931, v, 613–624.
14. Barker, N. W.: Tobacco factor in thromboangiitis obliterans, Proc. Staff Meet., Mayo Clin., 1931, vi, 65–68.
15. Maddock, W. G., and Coller, F. A.: Peripheral vaso-constriction by tobacco demonstrated by skin temperature changes, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 487–488.

    Maddock, W. G., and Coller, F. A.: Peripheral vaso-constriction by tobacco and its relation to thromboangiitis obliterans, Ann. Surg., 1933, xcviii, 70–81.
16. Harkavy, J., Hebald, S., and Silbert, S.: Tobacco sensitiveness in thromboangiitis obliterans, Proc. Soc. Exper. Biol. and Med., 1932, xxx, 104–107.
17. Sulzberger, M. B., and Feit, E.: Studies in tobacco hypersensitivity; thromboangiitis obliterans with positive urticarial skin reactions and negative reagin findings, Jr. Immunol., 1933, xxiv, 425–432.
18. Mitchell, S. W.: Philadelphia Med. News, 1872, iii, 81, 113; Am. Jr. Med. Sci., 1878, lxxvi, 17.
19. Barker, N. W., Brown, G. E., and Roth, G. M.: Effect of pancreatic tissue extract on muscle pain of ischemic origin (intermittent claudication), Trans. Am. Therap. Soc., 1933, xxxiii, 115–120.
20. Kramer, D. W.: Evaluation of various methods of investigating circulation in lower extremities, Am. Jr. Med. Sci., 1933, clxxxv, 402–420.
21. Starr, I., Jr.: Studies on circulation of feet in diabetes mellitus with and without gangrene, Am. Jr. Med. Sci., 1930, clxxx, 149–171.

    Starr, I., Jr.: Acetyl-β-methylcholine; its action on paroxysmal tachycardia and peripheral vascular disease, with discussion of its action in other conditions, Am. Jr. Med. Sci., 1933, clxxxvi, 330–345.
22. Scott, W. J. M., and Morton, J. J.: Differentiation of peripheral arterial spasm and occlusion in ambulatory patients, Jr. Am. Med. Assoc., 1931, xcvii, 1212–1215.

23. Pearse, H. E., Jr., and Morton, J. J.: Blood pressure in arteries of extremities in normal subjects and in patients with peripheral vascular disease, Am. Jr. Med. Sci., 1932, clxxxiii, 485–494.
24. Lewis, T.: Blood vessels of the human skin and their responses, 1927, Shaw and Sons, London.
25. Lewis and Grant: Vascular reactions of skin to injury; liberation of a histamine-like substance in injured skin; the underlying cause of factitious urticaria and of wheals produced by burning; and observations upon nervous control of certain skin reactions, Heart, 1924, 209–265.
26. Starr, I., Jr.: Change in reaction of skin to histamine as evidence of deficient circulation in lower extremities, Jr. Am. Med. Assoc., 1928, xc, 2092–2094.
27. Greenbaum, S. S., and Carnett, J. B.: Blood vessel visualization, Jr. Am. Med. Assoc., 1927, lxxxix, 2039–2041.
28. Allen, E. V., and Camp, J. O.: Diagnostic value of arteriography, with report of two cases, Minn. Med., 1934, xvii, 167–170.
29. Herrmann, L. G., and Reid, M. R.: Treatment of obliterative vascular disease by means of intermittent negative pressure environment, Jr. Med., 1933, xiv, 200–204.
30. Kovacs, J.: Iontophoresis of acetyl-beta-methylcholine chloride in treatment of chronic arthritis and peripheral vascular disease; preliminary report, Am. Jr. Med. Sci., 1934, clxxxviii, 32.
31. Doane, J. C.: Arch. Phys. Therapy, 1934, xv, 599.

MULTIPLE MYELOMA *

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The renewed interest in diseases of bone apparent in current medical literature had its impetus in 1926 when Mandl, in a crucial clinical experiment, established the etiologic relationship between tumor of the parathyroids and von Recklinghausen's disease of bone (osteitis fibrosa cystica). This removed the disease from the category of a morphologic to that of an etiologic entity, as demonstrated by the numerous reports of cases which followed. On the basis of both clinical and experimental study, Jaffe,[1] in his recent exhaustive review of the disease, indicates that the pathogenesis involves decalcification or demineralization of the skeletal system through the action of the increased parathyroid hormone secreted by the glandular tumor. The local bony changes are secondary to this process of resorption. The clinical features embrace the consequences of the skeletal changes and the resultant disturbed calcium metabolism.

A consideration of other conditions in which there is generalized bone destruction, especially osteoclastic carcinoma and multiple myeloma, indicates that these may simulate hyperparathyroidism. The former may lend itself to easy differentiation on the basis of a known primary cancer and characteristic roentgen-ray findings. Multiple myeloma, on the other hand, may be more difficult to differentiate. An instance of this disease which was clinically believed to represent hyperparathyroidism, with a postmortem study of the parathyroid glands, is the basis of this report.

Case Report

C. R., age 66, a machinist, first came under observation September 17, 1932, complaining of pain in the lower part of his back of three weeks' duration, which he ascribed to lifting an iron mold weighing about 60 pounds. The pain was dull, persistent, and much aggravated when he changed his position from sitting to standing, or on turning in bed. On further inquiry, he had also noticed loss of 30 pounds in weight and gradually increasing weakness during the previous year. The following additional information was elicited: His appetite was fair. He was troubled with frequent urination for two years, diurnal as well as nocturnal. There was no concomitant polydipsia. Constipation, which had been present for many years in mild form, had recently become more pronounced, so he resorted to enemas frequently.

Physical examination: The patient was 5 feet in height and weighed 126 pounds. He seemed normal mentally except for a slowing of his response to questions. He moved cautiously as if guarding against pain. The skin was dry, of poor texture, and showed no abnormal pigmentation. His blood pressure registered 136 systolic, 76 diastolic. On the skull was an irregular protuberance in the left occipital area due to an old injury, details of which the patient did not recall. Arci senilis were noted, but the eyes were otherwise normal in appearance and reaction. The teeth were out and replaced by plates. The throat appeared normal; the tonsils were recessed. The

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neck showed no abnormal pulsation, no thyroid enlargement, and no adenopathy. The chest was moderately emphysematous. The lungs and heart were normal except for the distant character of the heart sounds.

The abdomen was scaphoid. No organs or masses were palpable, nor were there any tender areas. The spine was moderately kyphotic in the dorsal region. On firm pressure, tenderness was elicited over the lumbar spine and right sacroiliac joint. The extremities were extremely emaciated, and the musculature flabby. The peripheral arteries felt tortuous and sclerotic. The fingers showed Heberden nodes. The knee-jerks were present.

On the basis of the history of pain in the back with disability, loss of weight and strength, urinary frequency, and tenderness over the lower spine and pelvis, the possibility of prostatic malignancy with bony metastasis was first considered. Rectal examination revealed a small, fairly firm prostate without sufficient hardness to be considered malignant. After voluntary voiding, the patient was catheterized for residual urine. No obstruction was encountered and no urine was obtained. Roentgen-ray examination of the lumbar spine and pelvis was inconclusive, being interpreted as showing osteoarthritis of the vertebrae as well as "areas suspicious of bone destruction of the vertebrae, pelvis, and upper ends of femora."

The patient's subsequent course was one of invalidism. He was virtually bedridden. He remained afebrile. The pain in his back was variable, though usually made severe by motion. He continued to be troubled with constipation and urinary frequency; the latter occasionally necessitated voiding every half hour at night. His appetite became poor. He often felt nauseated and vomited once or twice daily for periods of several days.

Hospitalization was advised for further study. During a period of six days his temperature range, pulse and respiration rates were normal. Another roentgen-ray examination was done at this time and showed "marked lime deficiency in vertebrae, pelvis, femora, and ribs," as well as a marked sclerosis of the arteries. A view of the skull showed a similar type of bone involvement. The red blood cells numbered 2,870,000 and showed a moderate degree of anisocytosis; hemoglobin 47 per cent. The leukocyte count was 7450, with polymorphonuclear neutrophiles 76 per cent, eosinophiles 1 per cent, lymphocytes 22 per cent, and monocytes 1 per cent. The blood Wassermann and Kahn tests were negative. The urine showed a trace to one plus albumin, 20 leukocytes per high-power field, and a few hyaline and granular casts. Bence-Jones protein was not found in one test. The stool examination revealed neither blood nor parasites. The blood chemistry showed the following: Glucose 125 mg., non-protein nitrogen 49 mg.; blood calcium on two estimations showed 11.8 mg. and 12.6 mg. as compared to a normal range of 9 to 11 mg. Two weeks later the blood calcium was 13.7 mg. and the blood phosphorus 3.2 mg. A determination of urinary calcium excretion in 24 hours gave a reading of 530 mg. on a diet containing approximately 200 mg. of calcium, indicating the likelihood of a negative calcium balance.

It was felt that there was sufficient evidence to warrant exploration of the neck for a parathyroid tumor. At operation, however, no tumor was found, but tissue presumed to be parathyroid after study of frozen sections was removed. Postoperatively the patient was subsequently observed for signs of tetany, but none were detected, and the serum calcium showed 13.5 mg. The day following the operation cough developed, the temperature rose to 103°, the pulse rate increased, and the local chest findings indicated basal bronchopneumonia from which the patient died on the third postoperative day.

Postmortem Examination: The body was that of an extremely emaciated white male, 5 feet 3 inches in length and weighing about 100 pounds. The immediate cause of death was a generalized acute purulent bronchitis and bilateral bronchopneumonia of the lower lobes.

Inspection of the skull revealed numerous discrete, sometimes confluent, areas of resorption between the outer and inner tables. These areas were translucent, although frequently they appeared to be somewhat hemorrhagic. The texture of the skull bones did not appear to be appreciably altered. The cut edges of the bones of the skull indicated that these areas of resorption consisted of soft, somewhat hemorrhagic and gray tissue of the consistency of soft butter. The bony surfaces around these areas were excavated or concave as though they had been eroded.

The ribs and sternum were soft, occasionally brittle, easily fractured and incised. Numerous centrally located lesions of hemorrhagic character could be made out, especially upon illumination of the bones. The bone marrow appeared to be replaced by this hemorrhagic tissue, which had eroded the cortex of the bone. The bone tissue was obviously decalcified and softened. The femora, pelvic bones, tibiae, and fibulae were involved by the same type of central lesion.

A most careful dissection of the neck tissues from the base of the tongue to the

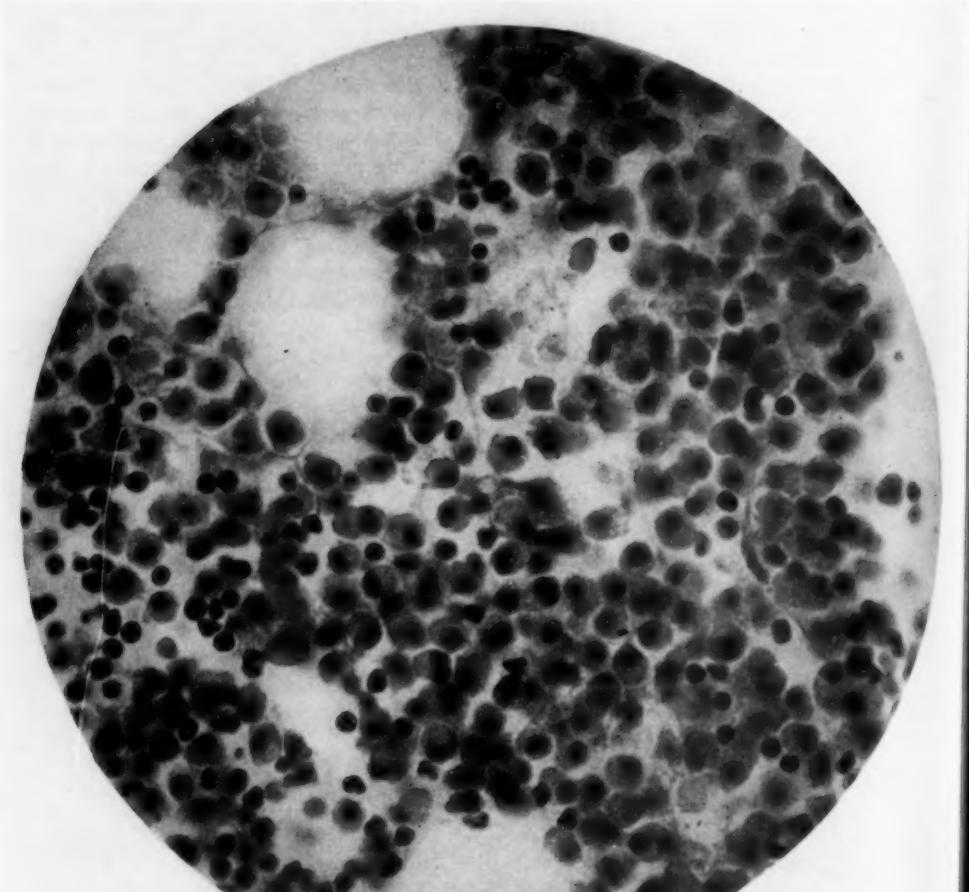

FIG. 1. Bone marrow showing diffuse myelomatosis.

mediastinum revealed no evidence of parathyroid tissue, nor did careful examination of thin serial sections of the thyroid.

Examination of thoracic and abdominal viscera and brain did not disclose any changes other than generalized atrophy and a moderate degree of atherosclerosis. The gall-bladder contained one stone.

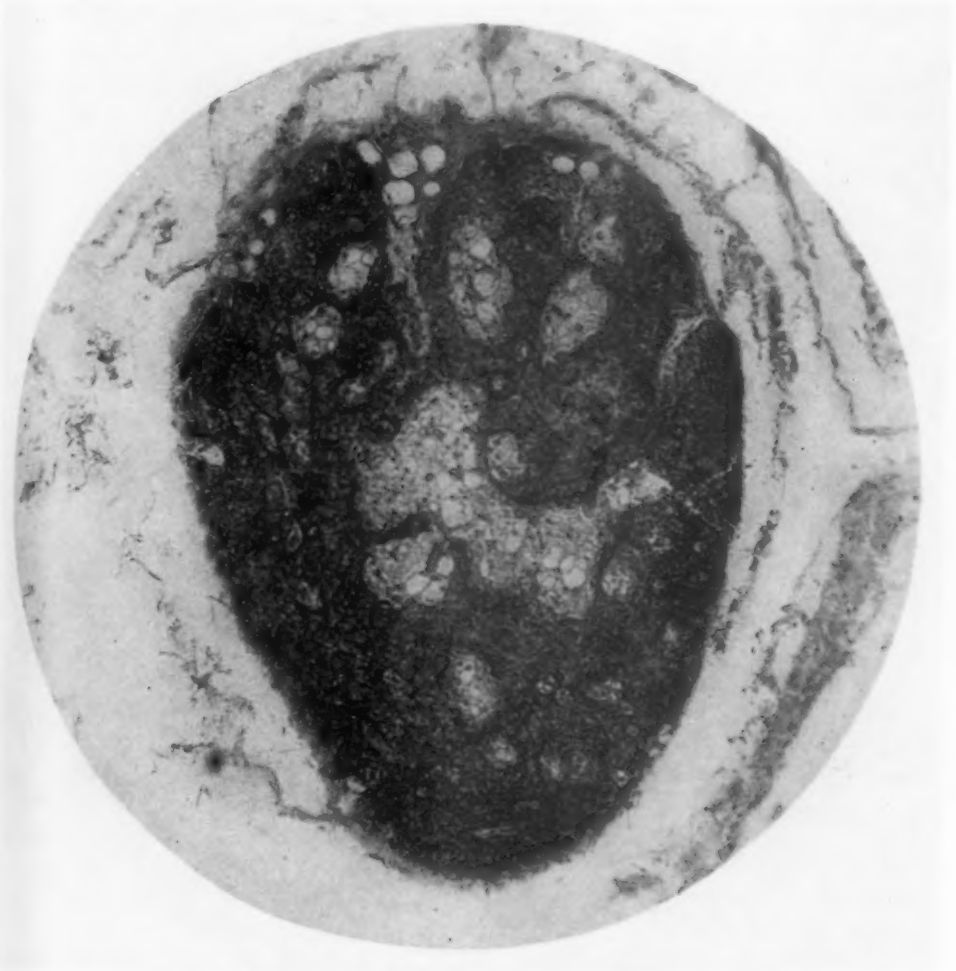

FIG. 2. Low-power magnification of parathyroid gland.

Microscopic examination of sections of the bones disclosed a diffuse and nodular tumor occupying the bone marrow (figure 1). The cells comprising the tumor were closely packed and remarkably uniform. The nuclei were round and usually eccentrically placed. The cytoplasm stained poorly and was homogeneous. A very occasional mitotic figure was found. Special staining revealed little or no connective tissue stroma. Small areas of atrophic fat tissue and fat cells were found between the tumor cells. Here and there between the tumor areas were moderately hyperplastic islets of myeloid tissue. These were particularly rich in erythroblasts, but the myeloid elements appeared to be normal. The bone cortex in all the bones examined

exhibited marked atrophy and consisted of slender fragments of slowly absorbing bone trabeculae. Occasional areas of recent and old hemorrhage were present in the tumor-bearing portions. Mild inflammatory reaction consisting of lymphocytes and occasional polymorphonuclears was present in the atrophic bone.

Numerous sections were made from tissue of the neck and thyroid. In one section only were we able to identify a parathyroid gland (figure 2). This was embedded in fat, and the gland itself was less in diameter than that of the low-power

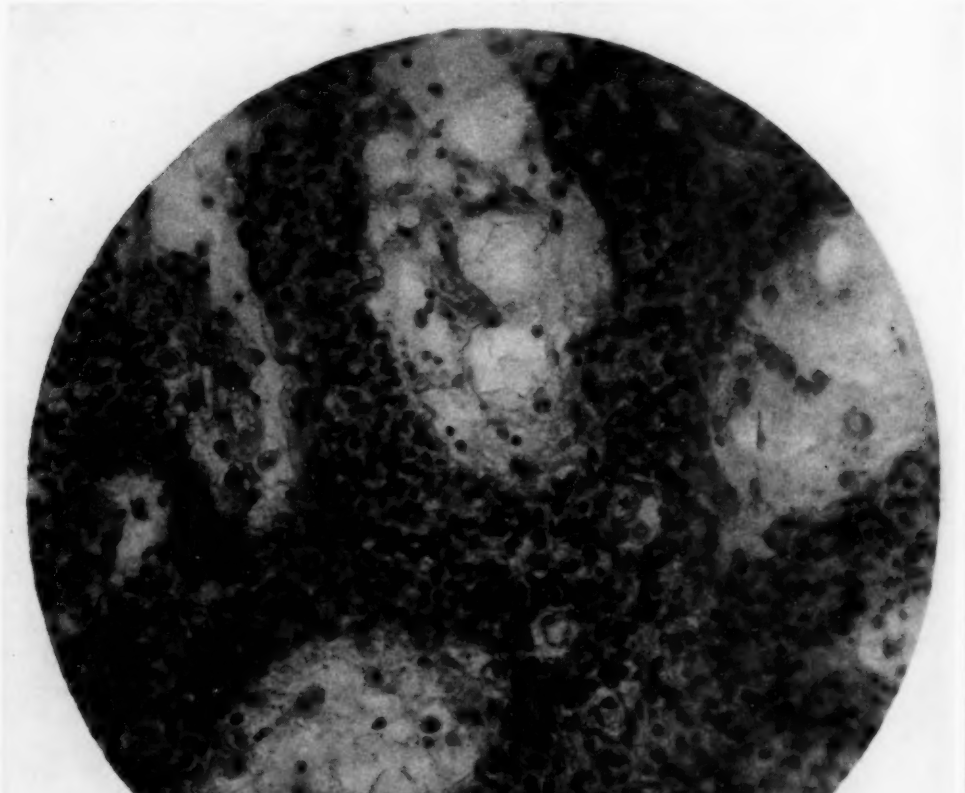

FIG. 3. High-power magnification of parathyroid gland.

field. The gland consisted of an encapsulated mass of cuboidal cells arranged in anastomosing chords, and separated by a loose areolar tissue containing fat (figure 3). Connective tissue was scant and the vascular network difficult to make out. The cells were uniform with oval and round vesicular nuclei surrounded by clear cytoplasm. There was no evidence of hemorrhage nor inflammatory reaction. The final diagnosis was generalized myelomatosis.

Two aspects of this case merit further elaboration: the relation of the parathyroid glands to multiple myeloma, and the similarity between the clinical features of this disease and hyperparathyroidism. Our interest was aroused in this instance by the absence of parathyroid tissue except as found in the microscopic sections. While it is appreciated that the glands may be situated in other than their usual sites, the dissection in this case was so thorough that the possibility of our having overlooked abnormally located glands is unlikely. Whether or not the glands in this patient were atrophic beyond that which is occasionally encountered in individuals of his age may reasonably allow for difference of opinion, but the case does indicate the compatibility of the absence of parathyroid hyperplasia with myelomatosis. Theoretically, it may be suggested that the glands are either unaffected by the disease, or undergo atrophy. To assume that because of the abnormal mobilization of calcium from the "skeletal storehouse," the parathyroids in this case were thrown into a functional, and later, into an anatomical atrophy, is as reasonable as the assumption that hyperplasia of the glands may be stimulated by the same process.

The latter conclusion was drawn by Bulger and Barr [2] from a case strikingly similar to ours, but considered clinically to have neoplastic disease of the bones. The serum calcium in their case was 16 mg. and phosphorus 3.7 mg. At necropsy myelomata of the plasma cell type were found in the vertebrae, ribs and clavicles, as well as metastatic calcification in the lungs, stomach mucosa, and kidneys. In three parathyroid glands definite hyperplasia was found. On the basis of their findings in this case, they presumed the existence of a state of "secondary hyperparathyroidism" due to hyperfunctioning of the parathyroid glands. They concluded that "many generalized diseases of bones accompanied by extensive absorption or destruction of bone substance, lead eventually to significant parathyroid hyperplasia." A different conception was held by Klemperer [3] who, in a case of skeletal carcinomatosis showing newly formed but uncalcified osteoid tissue, found a tumor of one of the parathyroid glands. He interpreted the hyperplasia as the structural expression of an inadequately functioning gland. In other cases of myeloma, Jores [4] and Peters [5] did not find any changes in the parathyroids. Jaffe [1] holds to the theory of a "compensatory reaction" as accounting for the enlargement of the glands in diseases other than von Recklinghausen's. He indicates that the pathogenesis or mechanism of such enlargement is not obvious, but he considers that it may be an attempt on the part of the glands to maintain a quantitative increase of the hormone to counteract the effect of calcium deprivations in these conditions. From these divergent views it may be concluded for the present at least, that anatomical hyperplasia or functional hyperactivity of the parathyroid as the result of disturbances of calcium metabolism due to intrinsic disease of bone, is not proved.

On the basis of their clinical features, and because of like alterations in

the calcium metabolism, Jores [4] was among the first to call attention to the similarity between multiple myeloma and hyperparathyroidism. He reported his findings in two instances of myeloma, with studies of the calcium balance, and emphasized the negative balance as in hyperparathyroidism. More recently, Caylor and Nickel [6] attest to the diagnostic difficulty encountered in a case of generalized osteoporosis with hypercalcemia in which the diagnosis of myeloma was finally based on a rib biopsy. That hypercalcemia may occur in myeloma is a long known fact, but that it may be absent in hyperparathyroidism has also recently been shown. Wilder [7] and Gutman [8] have reported cases in which the serum calcium was normal or only slightly increased in this disease. The presence of the Bence-Jones albumose in myeloma is neither a constant nor a pathognomonic feature. While the roentgenologic findings in the bones differ in the two diseases, it is significant that in the case above reported, a competent roentgenologist believed the lesions represented decalcification due to parathyroid overactivity. It becomes evident that one or two diagnostic procedures will yield insufficient information in a case belonging in this group of diseases, and that conclusions should be drawn only from comprehensive clinical, chemical, metabolic (calcium balance), roentgen-ray, and biopsy studies. This is all-important in the event of the possible discovery of hyperparathyroidism in its early phases with a chance for cure by surgical removal of a parathyroid tumor.

The clinical history and physical examination may yield important clues pointing to a direct diagnosis. While pain in various regions of the skeletal system, loss of weight and strength, gastrointestinal and urinary symptoms, muscular wasting, and spontaneous fracture are common to these diseases, the finding of a small tumor in the thyroid region should at once lead to a consideration of a parathyroid adenoma and warrant exploration if substantiated by the results of other examinations. The quantitative changes in certain of the blood serum constituents constitute the most important features in these conditions. In most cases of hyperparathyroidism there is a variable hypercalcemia usually in association with a normal or low level of serum phosphorus. The significance of a normal serum calcium, however, has been alluded to above. On the other hand, in many cases of myelomatosis the calcium level is appreciably elevated, although the phosphorus level is generally normal or slightly elevated. More recently an increase in the amount of the serum protein has been reported in cases of multiple myeloma by Wintrobe and Buell,[9] and by Reimann,[10] with the suggestion that this factor is intimately related to the nature of the disease. The globulin fraction, according to Peters,[5] is especially involved and it is in this disease in which it may show its greatest increase. The determination of the serum phosphatase, according to the method of Bodansky,[11] will yield increased values in hyperparathyroidism and normal values in myeloma.

From the standpoint of the calcium metabolism alone, the two conditions

herein considered are highly similar, both showing increased calcium excretion in the urine. In ordinary clinical work, studies of calcium balance with measured intake and output in urine and feces are not easily applicable. The diet suggested by Snapper [12] facilitates such a study when desired, since it entails only a determination of the calcium excreted by the kidneys.

The bone changes disclosed by roentgen-ray examination in these diseases may at times bear striking resemblances, depending on the degree of development of the disease. Camp [13] has recently delineated the characteristic changes in hyperparathyroidism. Confronted with roentgenograms presenting only a state of generalized osteoporosis, a differentiation is not readily made unless there be changes in the nature of cysts and giant cell tumors indicative of advanced von Recklinghausen's disease.

As a final and conclusive diagnostic procedure, biopsy of bone, either of rib, iliac crest, or by sternal puncture, as suggested by Custer,[14] may be resorted to in any case when indicated because of equivocal results yielded by other laboratory procedures.

Summary

A case report of multiple myeloma with clinical and laboratory features simulating hyperparathyroidism is presented. The possible rôle of the parathyroid glands in myelomatosis and other generalized bone disease is considered. In the case reported, parathyroid atrophy was encountered, and the concept of secondary or functional hyperparathyroidism is questioned. The similarity between myelomatosis and hyperparathyroidism appears to be on the basis of disturbed calcium balance common to both. The laboratory methods for differentiating between the two diseases are enumerated.

BIBLIOGRAPHY

1. Jaffe, H. L.: Hyperparathyroidism (Recklinghausen's disease of bone), Arch. Path., 1933, xvi, 63; 236.
2. Bulger, H. A., Dixon, H. H., Barr, D. P., and Schregardus, O.: Functional pathology of hyperparathyroidism, Jr. Clin. Invest., 1930, ix, 143–190.
3. Klemperer, P.: Parathyroid hyperplasia and bone destruction in generalized carcinomatosis, Surg., Gynec. and Obst., 1923, xxxvi, 11–15.
4. Jores, A.: Beitrag zur Differentialdiagnose des multiplen Myeloms und der Ostitis fibrosa generalisata mit besonderer Berücksichtigung des Kalkstoffwecksels, Klin. Wchnschr., 1931, x, 2352–2354.
5. Peters, J. P., and Eisenman, A. J.: Serum proteins in diseases not primarily affecting cardiovascular system or kidneys, Am. Jr. Med. Sci., 1933, clxxxvi, 808–833.
6. Caylor, H. D., and Nickel, A. C.: Multiple myeloma simulating hyperparathyroidism, Ann. Surg., 1933, xcvii, 823–827.
7. Wilder, R. M., Camp, J. D., Robertson, H. E., and Adams, M.: Fatal case of hyperparathyroidism with report of necropsy, Proc. Staff Meet., Mayo Clin., 1932, vii, 597–606.
8. Gutman, A. B., Swenson, P. C., and Parsons, W. B.: Differential diagnosis of hyperparathyroidism, Jr. Am. Med. Assoc., 1934, ciii, 87–94.

9. WINTROBE, M. M., and BUELL, M. V.: Hyperproteinemia associated with multiple myeloma, Bull. Johns Hopkins Hosp., 1933, lii, 156–165.
10. REIMANN, H. A.: Hyperproteinemia as cause of autohemagglutination; observations in case of myeloma, Jr. Am. Med. Assoc., 1932, xcix, 1411–1414.
11. BODANSKY, A.: Phosphatase studies, determination of serum phosphatase. Factors influencing accuracy of determination, Jr. Biol. Chem., 1933, ci, 93–104.
12. Cited by JORES.[4]
13. CAMP, J. D.: Osseous changes in hyperparathyroidism; roentgenologic study, Jr. Am. Med. Assoc., 1932, xcix, 1913–1917.
14. CUSTER, R. P.: Studies on structure and function of bone marrow; bone marrow biopsy, Am. Jr. Med. Sci., 1933, clxxxv, 617–624.

HYPERPROTEINEMIA, AUTOHEMAGGLUTINATION, RENAL INSUFFICIENCY AND ABNORMAL BLEEDING IN MULTIPLE MYELOMA *

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Multiple myeloma cases notoriously present bizarre clinical syndromes often diagnosed as arthritis, neuritis, severe anemias, or chronic nephritis, etc., depending on the predominance of various symptoms or findings such as pain, pallor, or urinary or blood nitrogen findings respectively.

Likewise many unique chemical and hematological findings are reported, most of which are neither entirely explained nor satisfactorily related to the underlying disorder. Reimann,[1] however, first called attention to the cause of the autohemagglutination seen in the blood of a patient who had been treated for arthritis for months. The fact that this patient's red cells formed tight rouleaux in smears and in a red cell pipette when Hayem's solution was used as a diluent, led him to suspect hyperproteinemia and, as a cause for this, multiple myeloma. His impression was correct as was proved at autopsy. Reimann rightly distinguishes autohemagglutination (marked rouleau formation) from true isoagglutination which is used in typing bloods for transfusions, although in the former clumps of great size may be formed which are distinguished with difficulty from clumps due to isoagglutinations. Bönniger [2] reports similar rouleau formation in smears and difficulty in counting red cells because of a precipitate forming with Hayem's solution, but not with salt solution. Serum from his patient still formed a precipitate, even when diluted 10 times. Both the above authors report marked clumping of donors' blood cells, when the serums of their patients were mixed with cells from various donors of the same isoagglutinin group, while the patients' red cells were not affected by serum of the same group. The sedimentation rate of the erythrocytes in Reimann's case was so rapid that complete settling had occurred in 10 minutes, and large macroscopically visible clumps were seen within the sedimentation period. Freund and Magnus-Levy [3] report six cases in the literature, including one of their own, in which the sedimentation rate was very rapid, and Bönniger's case showed the same phenomenon. Reimann, Bönniger, Freund and Magnus-Levy ascribe the rapid rate to the marked rouleau formation, and this in turn to the increase in the blood globulin and fibrinogen in their cases. Fahraeus [4] has proved the same in bloods of patients with various diseases by means of preparations of bloods and blood proteins in the test tube, and explains the rouleau formation as due to changes in the interface between

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TABLE I

Summary of Cases in Literature Showing Hyperproteinemia

Author	Year	Total Protein	Albumin	Globulin	Fibrin	Bence-Jones in Blood	Renal Insufficiency	Bence-Jones in Urine	Blood Calcium	Blood Phosphorus	Autohem-agglutination	Increased Sedimentation Rates	Red Cells in Millions	Reference
Jacobson, V. C.	1917	High				7.86%	Severe	0.7%					2.38	Jr. Urol., 1917, i, 167.
Pibram, H.	1925	8.7					Slight	4.5%						Med. Klin., 1925, xxi, 368.
Perlzweig, W. A. Delrue, G., and Geschickter, C.	1928	12.32 13.40 13.84	1.42 1.67 4.06	10.11 11.04 9.09	0.79 0.69 0.69	trace trace trace		+	10.8	4.8			1.80	Jr. Am. Med. Assoc., 1928, xc, 755.
Bannick, E. G., and Greene, C. H. (Case 2, Case 13).	1929 1929	9.00 10.54	2.50 4.45	6.50 6.09		+	++ Slight	+ +					1.83 3.60	Arch. Int. Med., 1929, xliv, 486.
Hubbard, R. S.	1930	8.94	5.56	1.74	0.79			13 gm.						Jr. Lab. and Clin. Med., 1930, xv, 554.
Bennhold, H. (Case a, Case b, Case c, Case e, Case f).	1931 1931 1931 1931 1931	11.40 9.50 8.00 16.00 14.00	1.80 2.60 3.60 1.20 6.20	9.60 6.90 4.40 14.80 7.90										Personal communications to Freund, R., and Magnus-Levy, A.: Ztschr. f. klin. Med., 1932, cxxi, 1.

TABLE I—(*Continued*)

Author	Year	Total Protein	Albumin	Globulin	Fibrin	Bence-Jones in Blood	Renal Insufficiency	Bence-Jones in Urine	Blood Calcium	Blood Phosphorus	Autohemagglutination	Increased Sedimentation Rates	Red Cells in Millions	Reference
Jores, A.	1931	9.30	3.30	5.80	0.19			+	18.0 20.0	3.47 4.04		++++		Klin. Wchnschr., 1931, x, 2352.
Reimann, H.	1932	10.12	0.90	3.84	5.48		Slight	0	18.0		++++	++++	3.10	Jr. Am. Med. Assoc., 1932, xcix, 1411.
Medes, G.	1932	16.00												Personal communication to Reimann.
Shirer, J. W., Duncan, W., and Haden, R. L. (Case 2).	1933 1933	13.78 11.37	2.44 2.44	11.34 8.93		7.85% 4.14%	+++ 0	0 +	14.1				3.24 2.84	Arch. Int. Med., 1932, l, 829.
Bönniger, M.	1933	13.00				0		0			++++	++++		Deutsch. med. Wchnschr., May, 1933, lix, 770.
Wintrobe, M. M. and Buell, M.	1933	11.90	2.50	?		?							3.29	Bull. Johns Hopkins Hosp., 1933, lii, 156.

the red cells and the blood serum, either by reducing the relative electric charge or by depriving the surface colloids of water.

In the literature relatively few references to the amount of blood proteins in multiple myeloma are found. Eighteen cases are found showing hyperproteinemia (total protein eight grams or over per 100 c.c. serum or plasma). (See table 1.) Freund and Magnus-Levy found that in about half of the 23 cases collected by them in which blood proteins were determined, figures higher than normal were found, and since then a case is reported by Barker [5] having a normal protein content. It is interesting to note (table 1) that in the cases showing hyperproteinemia the Bence-Jones protein output in the urine was absent or slight, and that, as Freund and Magnus-Levy point out, cases passing much Bence-Jones protein in the urine show low or normal total blood protein. The table also shows that the increase in serum protein is nearly always due to an increase of the globulin fraction, although Reimann's case showed a marked increase of fibrin.

In cases where the partition of the increased globulin has been studied, the euglobulin has been found to form the largest part of the globulin. (Perlzweig, Delrue and Geschickter,[6] Bannick and Greene,[7] Reimann,[1] Shirer, Duncan and Haden [8]). Freund and Magnus-Levy also report an extramedullary plasmoma with a normal total protein (7.3 grams) but there was a reduction of albumin to 3.6, and increased globulin to 3.7 grams. Marked increase in fibrin was present, also a very rapid sedimentation rate.

High serum protein values are extremely rarely found in other diseases. In severe dehydration the figures found in multiple myeloma are approached, and also in Kala azar in which Wu [9] found the highest figure 10.5 per cent total protein in one case and in this and other cases a marked increase in globulin as high as 7 per cent was found. Rowe [10] found 10.4 per cent total protein in a case of undiagnosed enlargement of the inguinal lymph nodes after long venous stasis, the highest in a large series of various diseases, and Loeper et al.[11] found 11 grams in a case of a malignant tumor of the kidney. In a very peculiar case of osteopathia osteopriva in a senile person, Reiche [12] found 11.4 grams total protein with 8.6 grams of globulin.

Jacobson,[13] and Shirer, Duncan and Haden [8] found a large quantity of protein which precipitated at 56° C. which they considered to be Bence-Jones protein, but Magnus-Levy, Perlzweig,[6] and Wintrobe and Buell [14] believe that this is not proved, since highly unstable euglobulin may be precipitated also. Wintrobe and Buell call attention to the fact that the temperature of precipitation and solution of a protein are not physical chemical constants for these are influenced by many factors such as the concentration of the protein itself, the hydrogen-ion concentration, and the quantity of the electrolytes and other substances present, such as urea. In the two cases of Shirer, Duncan and Haden, however, the protein coagulable at 56° C., after washing thoroughly, redissolved in water on boiling. Perhaps some of the discrepancies in the literature can be explained on the assumptions of Wintrobe and Buell that Bence-Jones protein is not a single chemical individual

but is a class of substances which exhibit a peculiar coagulation phenomenon, and that other influences such as mentioned above may determine the presence or absence of a precipitate at any given temperature. Similarly, Bennhold [15] states that the normal proteins of serum are not sharply divided but that as one increases the quantity of ammonium sulphate in salting out experiments, increasing amounts of precipitate result. In 21 other cases besides those in table 1, namely Weinberg and Schwarz [16] (three cases), Citron,[17] Short and Crawford,[18] Bannick and Greene [7] (three cases, including two of Walters), Mainzer,[19] Freund and Magnus-Levy (two cases), Ellinger,[20] Gabbe,[21] Zadek and Lichtenstein,[22] Abderhalden,[23] Hewitt,[24] d'Alloco,[25] Decastello,[26] Donetti,[27] Marcovici,[28] Karlins and Lundquist,[29] protein coagulating at 56° C. has been reported. Freund and Magnus-Levy believe that many of these precipitates are due to fibrinogen and not to Bence-Jones protein.

Two cases showing much more bizarre findings are reported by Wintrobe and Buell,[14] and Karlins and Lundquist. In the plasma of the first case, in a hematocrit a layer of dense yellow precipitate one cm. high was found, composed microscopically of brown masses varying in size and appearing very viscid. When the tube was put on the ice overnight a cloudy white precipitate occurred throughout the plasma. This disappeared on exposure to room temperature and reappeared on cooling. This precipitate after purification was coagulated in faintly acid solutions at 40° C. but did not disappear on boiling. Complete fractionation of the proteins of this plasma was not possible because of the spontaneous precipitation. Karlins and Lundquist's case showed a fine milky precipitate just above the layer of blood cells, almost equal in volume to the blood cells when blood was treated with trichloracetic acid. When this precipitate was washed thoroughly and heated with water, complete solution of the material occurred, but then it did not reappear on cooling. It precipitated, however, on adding sulphosalicylic acid, disappeared on boiling and reappeared on cooling.

For many years much dispute has arisen as to the cause of the renal insufficiency found in many cases of multiple myeloma. Various pathological descriptions of the kidney are recorded, oftentimes far from explaining the azotemia satisfactorily. In a recent article Bell [30] has summarized most of the cases in the literature in which renal changes are mentioned and he concludes that in some the impairment has been due to arteriosclerotic changes, pyelonephritis, or prostatic hypertrophy. Other cases, including most of his own, showed as the only direct effect of multiple myeloma, formation of tubular casts of Bence-Jones protein which occluded the tubules and led to tubular atrophy. When large numbers were occluded, extensive atrophy of the cortex and renal insufficiency ensued. In one case furnished him by me (Case 3 of the series below) he concluded that the renal insufficiency was apparently caused by the accumulation of a highly concentrated protein in the glomerular capillaries, and in two other instances the same appearance was found in a few capillaries. This observation has never been mentioned

in other reports. In Bell's report the cases showing the atrophy due to tubular occlusions by casts and the case of Mainzer were those in which large amounts of Bence-Jones protein were excreted.

Abnormal bleeding and clotting seem to be uncommon in this disease in spite of the marked involvement of the bone marrow. Of all the reports reviewed for this article the only case in which this phenomenon occurred is in the one reported by Wintrobe and Buell, who mention prolonged bleeding time, and that the blood did not clot properly. At this time their patient's platelets numbered 108,000, whereas some time previously the platelet count had been 146,000. Citron, Perlzweig et al., and Reimann, report that only a very small amount of serum was expressed by the clot, and sufficient fluid for analysis could be obtained only by mechanical pressure of the clot. Citron's case and one of Freund and Magnus-Levy showed extremely prompt clotting, so that preparations for counting cells could not be made or were made with difficulty.

The following four cases represent the last four consecutive myeloma patients seen by the author. They show most of the queer clinical and chemical findings mentioned above.

Case I

W. C., male, forest ranger, age 44, was first seen by Dr. R. W. Kraft on November 27, 1933 complaining of pain in the lower portion of his back, and marked loss of strength and color, dating back to the latter part of June 1933, from which time the symptoms had become progressively worse. By September of the same year he was markedly anemic and had to rest after walking a block or less, and any exertion made him dyspneic and produced dull pain in his legs. After a few minutes' rest the pain in the legs would disappear and he would feel fairly comfortable. About November 15, 1933 a strenuous automobile ride over rough roads was followed by severe pain in the lower dorsal region of his spine. The pain had been continuous until he was admitted to the Pasadena Hospital on December 11, 1933. There were no other complaints worthy of mention.

On examination he was well nourished, markedly pale, the pulse was 90, respiration and temperature and blood pressure normal. There was a faint systolic murmur (hemic ?) heard at the base of the heart. The lungs were clear. The abdomen showed no masses or tenderness and the spleen and liver were not palpable. The prostate was not remarkable. There was slight tenderness over the sixth dorsal spine. The lymph nodes throughout the body were not enlarged and there were no swellings noted on any of the bones. No edema was present.

The blood counts are given in table 2. The red cells were on the average slightly smaller than normal and varied slightly in size and shape; some were well filled with hemoglobin while others were moderately pale. Some of the polymorphonuclear leukocytes showed toxic granulation. On all smears occasional immature granulocytes were seen, as well as a few normoblasts and rarely a megaloblast. The smears showed also marked rouleau formation of the red cells (figure 1A) even in the thin portions, and wet films of oxalated blood showed large clumps of erythrocytes (figure 2A). Grossly visible clumps of red cells occurred in a sedimentation tube, and within 10 minutes the entire column of red cells had settled completely. The patient's serum caused marked clumping (figure 2B) primarily due to profound rouleau formation, with several suspensions of red cells from donors of the same blood group as the

TABLE II

Hematologic Studies in Cases Reported in Text

	Date	Hb %	Reds in millions	Whites in thousands	Myeloblasts	Promyelocytes	Myelocytes	Polymorphonuclears			Eosinophiles	Basophiles	Monocytes	Lymphocytes	Plasma cells	Platelets in thousands	Venous clotting time (10 mm. tube)	Venous clotting time normal control	Bleeding time (Duke's method)	Prothrombin time	Prothrombin time normal control	Clumping in Hayem's solution
								Juveniles	Staff forms	Segmented												
Case 1, W. C.	11–27–33	20.7	1.280	3.9	2	2	½	6	8½	41½	¼	0	9	28½	1½				10′			0
	12–11–33	20.5	1.050	7.2	½	1½	1	1	6	51	0	0	6	33	0	red.	91′	32′	6′			0
	1– 3–34	38.5	2.225	4.5	1	0	1	1	6	35	2	0	15	33	3				5′			0
	2–21–34	32.8	1.810	4.0	4	1	1	3	11	17	15	1	17	27	3	140.	46′	41′	5′			0
Case 2, J. C.	2– 8–34	40.0	1.960	3.2	½	1½	2	1	5	43	0	0	3	42	2	98.	330′	25	30+′			0
Case 3, J. McM.	11– 9–31	34.7	2.040	6.5	0	0	0	1	76		0	0	4	19	0	298.	140′	22′	30+′	13′	5′	+
Case 4, M. C.	9–24–28	17.0	1.620	5.6	0	0	2	tot. 48			0	0	3	47	0	o. k.						+
	10– 2–28	32.0	1.810	6.0	0	0	1	tot. 50			1	0	5	43	0	90.						+
	10–28–28	29.0	1.780	6.3	0	0	3	tot. 55			1	0	5	36	0	160.						+
	11–12–28	32.0	1.510	5.0	0	0	rare	tot. 68			rare	0	1	31	0	64.						+

patient (Group IV Moss). This phenomenon was present at dilutions of one to four but not at one to eight of the patient's serum, at which dilution the serum was capable of causing isoagglutination of Type II and Type III cells. As noted in table 2, there was a marked delay in the clotting time of the venous blood and at one time

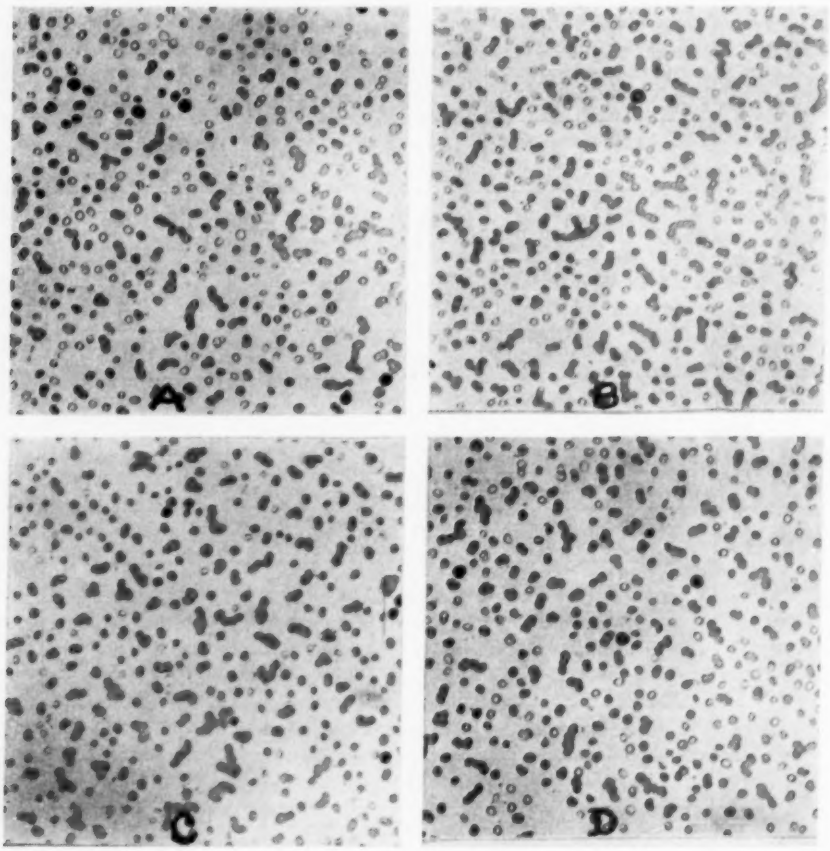

FIG. 1. Wright stained smears of blood, showing marked rouleau formation. *A*. Case 1. *B*. Case 2. *C*. Case 3. *D*. Case 4.

moderate increase in bleeding time. There was no coagulation of blood serum at 56 or 60° C. for an hour in a water bath. At about 70° slight clouding occurred in the tube, as well as in one containing serum from a normal person. Bence-Jones protein was therefore considered to be absent from the blood serum. Numerous samples of urine, about 12 in all, were tested for the presence of Bence-Jones protein, and none was demonstrated. Only occasionally was a trace of albumin found and on occasions a few granular and hyaline casts. Specific gravity varied from 1.015 to 1.026. Blood chemistry reports are given in table 3. There was marked increase in protein, due largely to an increase in globulin and about one and one-half to two times the normal fibrin was present. A marked increase in uric acid without change in the non-protein-nitrogen was also seen. Also, a moderate increase in blood calcium was demonstrated. The possible diagnosis of multiple myeloma was suggested; roentgen-rays were taken on December 19, 1933 and showed numerous closely packed areas of diminished density involving the entire cranial vault and some of the upper

ribs. The largest of these areas was less than one cm. in diameter and most were considerably less. There was moderate collapse of the sixth dorsal vertebra. There

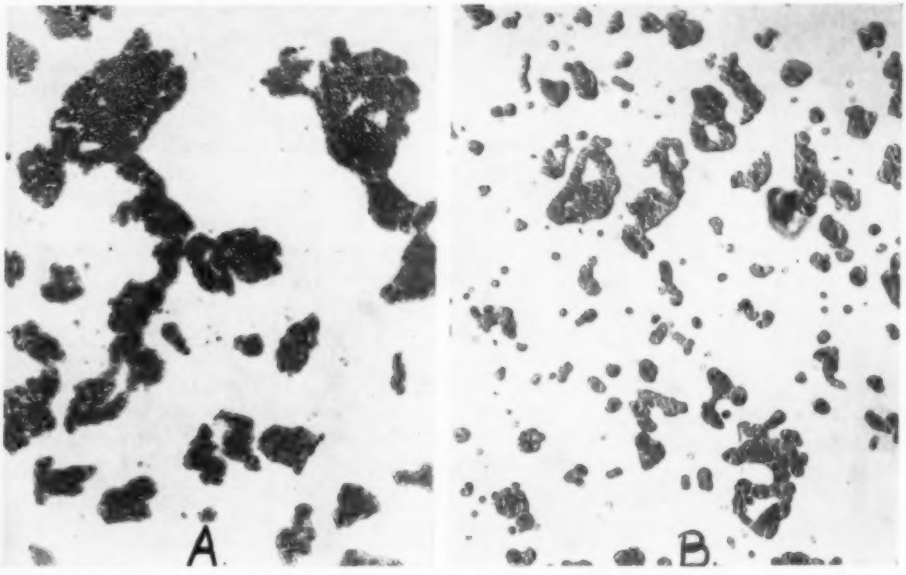

FIG. 2. Case 1. *A*. Wet film of oxalated blood of patient showing profound hemagglutination. *B*. Wet film of red cells of compatible donor plus patient's serum diluted 1 to 4, showing marked hemagglutination.

was no convincing evidence of any involvement of the long bones of the extremities. The findings were reported as being consistent with multiple myeloma.

A bone marrow puncture was made in the upper part of the sternum on December 18, 1933 and smears and sections of the gray-red fleshy fragments received showed

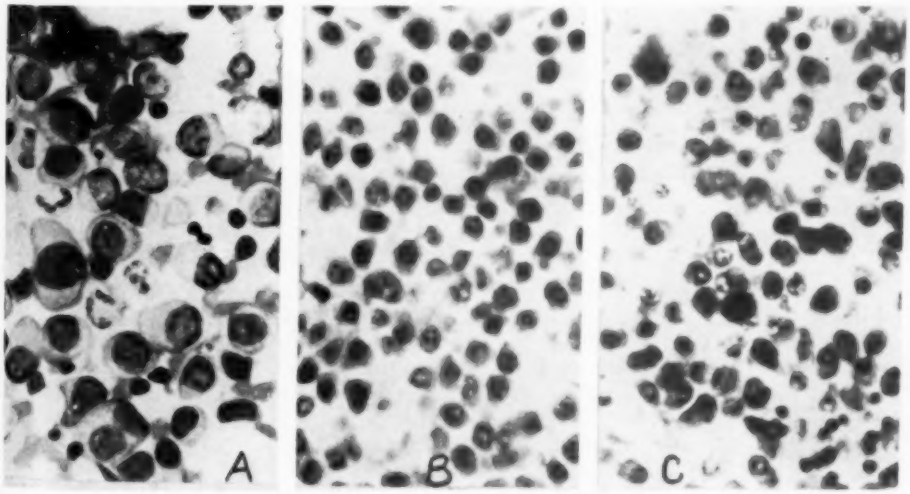

FIG. 3. *A*. Wright stained smear of marrow from sternum of Case 1, showing typical plasma cells. *B*. Section of myeloma from vertebra (Case 2) showing plasma cells. *C*. Section of marrow from femur of Case 3, showing plasma cells.

TABLE III

Blood Chemistry in Cases Reported in Text

	Date	Grams per 100 c.c. plasma				Milligrams per 100 c.c. of blood					CO_2 Volume %	Milligrams per 100 c.c. of serum	
		Total Protein	Albumin	Globulin	Fibrin	Non-Protein-Nitrogen	Uric Acid	Creatinine	Sugar	Chlorides (Whole Blood)		Calcium	Phosphorus
Case 1, W. C.	12–19–33	13.2	4.3	8.30	0.60	33.3	4.3	1.7	115	430	47%	12.6	4.6
	2–21–34	10.8	4.2	6.18	0.42	31.6	8.8	1.8	124	530	49%	12.2	3.6
	5–10–34	10.8	3.4	7.10	0.30	32.0	10.0	1.6	101	530		12.0	3.1
Case 2, J. C.	2– 5–34	15.0	5.5	8.80		160	12.0	5.5	133	524	48%	20.0	
Case 3, J. M.	11–11–31					100	4.0	2.9	111	509	45%		
	11–16–31				0.410	200	10.0	5.0					
Case 4, M. C.	9–20–28					Urea N 14.0	5.16	2.5		Plasma Chlor.			
	10– 2–28	11.37	1.86	9.51		25.4							
	10–13–28	11.51	1.57	9.94									
	10–26–28					35.6		2.46	126	680			
	11– 5–28	13.21											
	11–10–28					27.3				640			

a more or less diffuse growth through the marrow of plasma cells (figure 3A). Typical eccentric nuclei which were nearly spherical were seen and typical clumping of chromatin noted in many, producing a "watch-face" appearance. Many were obviously immature and in these the chromatin was more diffusely spread through the nucleus. These cells had replaced most of the normal bone marrow cells and by count fully 80 per cent of the cells were plasma cell types. The diagnosis of "plasma cell myeloma" was made.

On May 11, 1934, firm pressure was applied to the eyeball while the retinal vessels were studied with the ophthalmoscope. When the pressure was sufficient to stop the circulation in the arteries, the venous flow was very sluggish, and large red granules slowly following one another along the course of the veins were seen, resembling the aggregates seen in the sedimentation tubes. Without pressure this phenomenon could not be seen. It was not present in the eye of the author. The observations, first made by Dr. L. L. Henninger, were verified by Dr. George Dock who saw this patient several times in consultation, and myself.

The patient was given several transfusions and was allowed to be up and around with a leather support for his back. Deep roentgen-ray therapy was given over the spine and he was free from pain thereafter. About the middle of March he noticed some difficulty in locomotion and was put to bed with a back brace, and after a few weeks was allowed to get up gradually. Several transfusions were given which increased his blood hemoglobin and red cells temporarily, but within a period of two weeks following each transfusion, the blood had slumped to its previous level. He was discharged from the hospital unimproved on May 12, 1934.

Case II

J. C., male, age 68, was first seen in the office of Dr. H. B. Rickabaugh on January 11, 1934, complaining of severe pain in the right hip and in the lower part of the back, which was first noticed by the patient two months previously and had become progressively worse. Slight pain was also felt in the right side of the chest. He had also some loss of weight and strength. There were no other complaints. His family and past history revealed nothing of interest, except that he had suffered from some backache for three years.

Physical examination revealed an elderly man, fairly well nourished but showing a moderate pallor. There was marked pyorrhea but otherwise the head and neck were negative. The heart was not enlarged, but the tones were somewhat feebler than normal. Examination of the lungs was negative. The abdomen showed no masses, distention or noteworthy tenderness. The liver and spleen were not palpable. There was tenderness on firm pressure over the lumbar vertebrae and in the region of the right hip and along the upper portion of the course of the right sciatic nerve. There was no edema. The pulse, temperature and respiration were normal and the blood pressure was 108/80. The blood examination showed 45 per cent hemoglobin, 2,500,000 red cells and 5,400 white cells. The diagnosis of a rheumatoid infection was made and the patient treated by diathermy at the office, and symptomatically. On February 1, 1934 constant oozing from the gums began, which could not be stopped, and the patient was sent to the Alhambra Hospital. A transfusion of 500 c.c. of blood was given, but the bleeding continued.

Several urine samples showed specific gravity of about 1.015, protein +, sugar negative, and many hyaline and finely and coarsely granular casts; a few leukocytes and renal epithelial cells, but no red cells. A faint trace of Bence-Jones protein was demonstrated by acetic acid, sodium chloride and heat test, and by Exton's sulphosalicylic acid reagent. Most of the protein was serum protein which did not dissolve on boiling, but the Bence-Jones protein did, and after the coagulated serum protein was filtered off while still hot a faint cloudiness occurred on cooling. The amount was so small that it might have been missed easily if not carefully searched for.

The hematological studies conducted at the hospital are partly included in table 2. The red cells showed marked rouleau formation, even in thin parts of properly made smears (figure 1B). There were no noteworthy changes in the individual red cells except for rare polychromatophilic cells. A few of the neutrophiles showed toxic granulation. The platelets were normal. Wet films of fresh and oxalated blood showed marked clumping, exaggerated rouleau formation, and the clumps could be broken by pressure on the cover glass only to reappear immediately after the agitation was stopped. Grossly visible cayenne pepper-like clumps of red cells were formed within one minute after setting up a 200 mm. sedimentation tube, and within 15 minutes sedimentation was complete. There was marked prolongation of clotting time to five and a half hours in a 10 mm. paraffined tube. The cells settled promptly and the supernatant fluid formed a jelly-like mass which did not contract in 48 hours, and only after much manipulation only one-half c.c. of serum could be expressed from four c.c. of blood. The patient was a Type III (Moss), and his serum undiluted or diluted one to two caused marked hemagglutination of cells of three donors of the same group, suspended in 1½ per cent sodium citrate in normal saline. Dilutions to one to four were sufficient to inhibit this phenomenon. The red cells of the patient showed no abnormal response when mixed with various sera.

The blood chemical studies are included in table 3. In addition, tests for Bence-Jones on the serum were doubtful. No precipitate resulted after heating for one hour at 56° C. At 60° C. there was a minimal cloudiness, considerably heavier precipitate at 70° C. than with normal sera controls, and at 78° complete solidification occurred.

Roentgen-rays, suggested after the blood and urine studies were made, showed widespread involvement of the skull, vertebrae, ribs, clavicles, pelvic bones, sternum, typical of multiple myeloma, and a few punched out areas of decreased density were seen in the femurs.

The diagnosis of multiple myeloma was made. The patient went progressively down hill, and left the hospital for his home after a week's stay. He became stuporous, bleeding from the gums continued, and death occurred in coma on February 18, 1934.

Consent for autopsy was not obtained until partial embalming had been done. The essential findings were as follows: The entire vertebral column, the ribs, clavicles, sternum, bones of the pelvis and skull showed numerous gray-white fleshy tumors varying from a few millimeters to several centimeters across, destroying the part of the bone involved. The last lumbar vertebra was nearly entirely replaced by tumor, and tumor had perforated the periosteum and extended into the soft tissues about the bone. Some of the vertebrae and ribs were so involved that they could be readily cut with a knife. Numerous tumor nodules and a diffuse gray growth were seen in the marrow of the femur occasionally eroding the cortex of the shaft. The kidneys were swollen, weighed together 340 grams, were soft and flabby, cut easily, and the sectioned surface bulged under the capsule. The parenchyma was pale and opaque. The capsules stripped readily leaving a smooth, gray, dull surface. The spleen weighed 240 grams and the pulp was moderately softer than normal and dull pink in color. The liver weighed 1800 grams, was pale, and the markings just visible. The other organs showed chiefly anemia, except the lungs, which were marked by hypostasis and edema. The thyroid and parathyroids were normal. The lymph nodes were not enlarged.

Histological study of the bone tumors showed them to be made of solid masses of plasma cells with typical round eccentrically placed nuclei and a moderate amount of cytoplasm (figure 3B). Some showed typical "watch-face" distribution of chromatin, but others much more hyperchromic nuclei, and many showed mitoses. Smaller foci of similar cells were present throughout many marrow sections. Many plasma cells of the same types were found in the spleen, a moderate growth was also seen in the lymph nodes, and a rather pronounced proliferation of similar cells was

found in the liver, both in the interstitial tissue about the periportal channels as well as in the sinusoids of the lobules. A few were found in capillaries in various organs. The kidneys showed changes similar to those in Case 3 below and also a few foci of plasma cell proliferation, and there was a diffuse edema of the stroma. Only a few casts were found in the collecting tubules. The convoluted tubules showed flattening of the cells and moderate granular degeneration. Vascular changes were slight. The glomeruli showed neither endothelial proliferation nor thickening of the basement membranes. The capillary loops were filled with a thick protein precipitate and only occasionally was a loop seen containing blood cells. In a few the afferent arterioles were engorged with blood, but the loops contained only protein, giving the appearance of obstruction of the loops by the protein.

The final summary was: widespread multiple myeloma; renal insufficiency due to glomerular obstruction; plasma cell growth in liver, spleen, lymph nodes, and kidneys; severe anemia, hypostatic hyperemia and edema of lungs.

Case III

J. M., male, 52 years of age, was admitted to the Pasadena Hospital under the care of Dr. J. B. Luckie with the following history: He had suffered an acute illness in January 1931 which was diagnosed influenza by another physician. He had never quite recovered his strength and capacity for hard work following this, and had been going to his physician chiefly because of loss of strength and energy until October 1931, when he was told that he had anemia and that he would do better if his teeth were extracted. Eleven teeth were extracted and bleeding began immediately and continued in spite of the fact that his dentist gave him horse serum subcutaneously. He continued to bleed for about three weeks, when he was first seen by Dr. Luckie, who treated the gums locally and injected thromboplastin without any effect on the bleeding. He was admitted to the Pasadena Hospital November 9 and died eight days later. On examination he appeared very weak, markedly anemic; there was some bleeding from the nose, much bleeding from the gums, and crusts of blood were present on the lips and about the gums. The heart was not enlarged, and the lungs and abdomen were not remarkable. There was no evidence of purpura in any part of the skin. The lymph nodes were not enlarged. The temperature was normal, the pulse 108, and the blood pressure 165/110. There was no edema at any time.

During his stay at the hospital he continued to ooze from the gums in spite of intravenous calcium and one transfusion on November 12 of 500 c.c. of blood. During the last few days of life he was in a marked coma, Cheyne-Stokes breathing occurred on November 16, and he died on the seventeenth.

Six urinalyses showed a specific gravity of 1.011 to 1.017. There was always one to two plus protein, as demonstrated by Exton's sulphosalicylic reagent. This was not heated to boiling, and Bence-Jones protein was not sought for. In all specimens there were many hyaline, coarsely and finely granular casts, and a few renal epithelial cells. Only rarely were red cells and occasional leukocytes found. The blood findings are included in table 2. Clumping of the red cells in masses mixed with protein occurred in pipettes, using Hayem's solution as a diluent. Citrated saline was satisfactorily used. Examination of the smear showed a moderate achromia of the red cells and as in the preceding cases, a marked rouleau formation, even in the thin parts of the film (figure 1C). Only slight evidence of regeneration was seen. The polymorphonuclear neutrophiles showed a marked shift to the left, and some toxic budding was seen. No immature granulocytes were found. There was profound acceleration of the sedimentation rate, and bleeding from puncture of the ear was as marked at the end of 20 minutes as at the start, and was controlled by pressure. Marked prolonged clotting time and prothrombin time were found. Addition of three drops of 5 per cent calcium chloride to uncoagulated plasma failed

to accelerate clotting. The serum of this patient caused marked rouleau formation with cells of donors in the same blood group (Group IV Moss). The blood chemistry findings are given in table 3. It is regretted that the blood proteins other than the fibrin were not studied. The clinical diagnosis was always in doubt and multiple myeloma was not suspected. He was considered to be a case of atypical chronic nephritis.

An autopsy was done the day following death and the body had been embalmed by arterial injection. Briefly, the major points of interest were as follows: Throughout the vertebrae, ribs, sternum, and shaft of the right femur the marrow was markedly hyperplastic, red-gray in color, and in the femur could be removed in chunks without breaking. There was only slight absorption of the bony trabeculae in the vertebrae, ribs and sternum and no distinct tumor or enlargement of any of these bones could be seen. Grossly the appearance resembled markedly that of a leukemic process.

The kidneys weighed together 380 grams, were markedly swollen, cut easily, and felt soft. The cortex was about 9 mm. thick. It was gray, opaque, and the striations were just visible. The capsules stripped readily leaving a perfectly smooth surface. The spleen was normal in appearance, and the liver not remarkable. There was no enlargement of the lymph nodes. A slight bronchiectasis was found in the left lower lobe. The heart was moderately hypertrophic and weighed 450 grams. The valves were normal. There was minimal sclerosis in the coronaries and other arteries. There were no noteworthy changes in the thyroid or parathyroids.

Histologic examination of the bone marrow in smears and sections showed a nearly complete replacement of normal bone marrow by a diffuse growth of plasma cells showing typical eccentric, spheroid nuclei with an abundant cytoplasm; in many of the plasma cells vacuolization and granular degenerative changes were found (figure 3C). Most of the cells showed a typical "watch-face" distribution of chromatin and only a few showed immature nuclei. There was practically no absorption of the bone trabeculae in the sections made of the vertebrae, the growth appearing to grow diffusely through the marrow. There were no infiltrations in the spleen, liver, kidneys, or lymph nodes. The kidneys, a description of which is included as Case 86 in Bell's article,[30] showed as the principal finding a marked precipitation of protein in the glomerular capillaries, all of which were distended. The basement membranes of the capillary loops were not thickened; there was no endothelial proliferation, and in only a few of the loops were some red cells found and these failed to show evidence of clumping. The body had been embalmed and the red cells were apparently diluted by the washing-out fluid used, or possibly, as Bell suggests, the capillaries were obstructed by the concentrated plasma, which would naturally be more concentrated in the glomerular capillaries, where filtration of water takes place. There were only occasional casts found in the tubules and diffuse interstitial edema was present through the entire cortex; most of the convoluted tubules showed flattening of the epithelium, but minimal degenerative changes were present (figure 4). The rest of the organs presented nothing of interest except the lungs, which showed a profound edema and hyperemia of the alveolar walls. The protein precipitate in the lumina of the alveoli was very dense, much more so than that seen in a case with normal blood protein. Clumping of erythrocytes was not demonstrated in any of the organs, but this also may have been due to the dilution in the process of embalming. The final diagnosis was diffuse myelomatosis with renal insufficiency, due to blocking of the glomerular capillaries.

Case IV

M. C., Italian housewife, age 55, entered the Buffalo City Hospital September 19, 1928. The history was obtained through an interpreter. She complained of an

increasing weakness, loss of appetite, and anemia for the past nine months. She had had occasional dizzy spells during this period and occasional headache. There had been no vomiting, or pain in any part of the body, and inquiry as to symptoms referable to the various systems was negative except for those above mentioned.

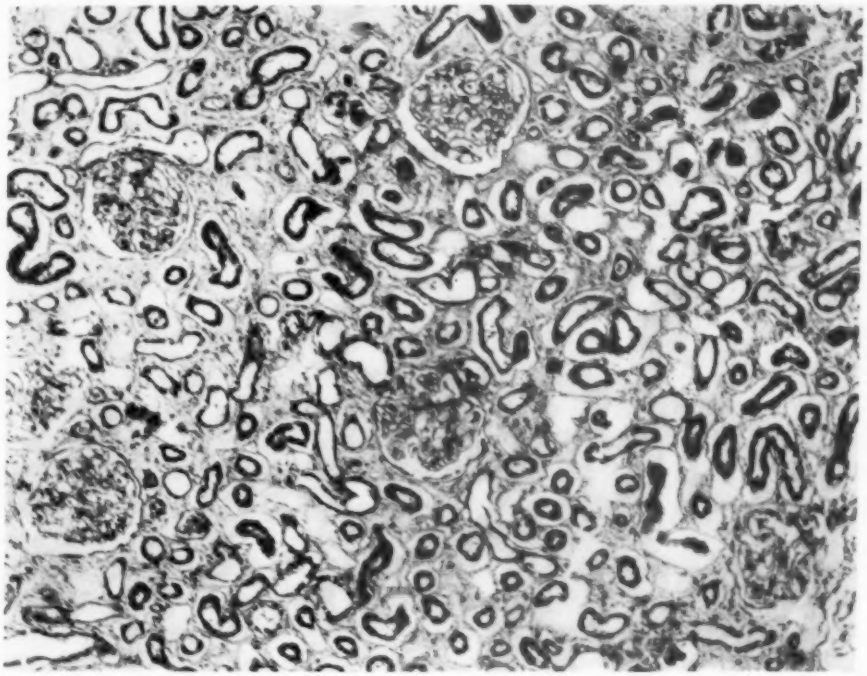

FIG. 4. Case 3. Kidney section showing edema of stroma, dilated tubules and glomerular capillaries dilated.

On examination she showed marked pallor and evidence of considerable loss of weight. There was no edema. Examination of the heart, lungs, abdomen and extremities was essentially negative, as was also the vaginal examination. No cause for bleeding was found. Two gastrointestinal series failed to reveal any evidence of disease. She was given several small transfusions but she failed to respond to these and finally left the hospital eight weeks after admission. Treatment of any kind was given with great difficulty because of her inability to speak English. Death occurred at home a few months later. No autopsy was permitted.

Laboratory examinations while this patient was in the hospital were as follows: The urine examinations showed a specific gravity of 1.012 to 1.014, occasionally 1.016 to 1.018, and no sugar. There was always a two to three plus protein, as demonstrated by Exton's sulphosalicylic reagent. Multiple myeloma was not suspected and no tests for Bence-Jones protein were made. The sediment showed occasional finely and coarsely granular casts and some waxy and hyaline casts. Phenolsulphonephthalein excretion in two hours was 35 per cent. The blood pressure was 125/70; the blood Wassermann test was negative, and the basal metabolic rate was plus 11 per cent. The hematologic findings are included in table 2. The red cell counts were all made with citrated saline as a diluent, since marked precipitation occurred when Hayem's solution was used. The smears showed marked rouleau formation (figure 1D) even in the thin portions; the cells averaged considerably smaller than normal in

size and showed a moderate achromia. There was very little evidence of regeneration. The polymorphonuclears at all times showed a moderate shift to the left with some toxic budding. The blood chemistry findings are included in table 3. There was no coagulation of the serum in heating at 56° C. for half an hour. The significance of the rouleau formation and the hyperproteinemia were not appreciated at the time, and the patient was discharged with a diagnosis of atypical chronic nephritis with secondary anemia.

The first clue to the diagnosis in the first two cases was presented by examination of the blood smear, which showed a most marked rouleau formation in even the thin parts of the film, although they were made promptly and dried quickly. The diagnosis was made presumptively in the second case before learning anything about the patient except that he had severe anemia and spontaneous bleeding without fever. Suggested chemical studies and roentgen-ray studies corroborated the first impression. The same rouleau formation in smears and the clumping of the red cells in Hayem's solution in the red cell pipette was noted in the third case but not understood at the time, and the diagnosis was not made until the autopsy. Likewise the fourth case was not recognized immediately in spite of the same phenomena in the red cells and the marked hyperproteinemia, the significance of which was not appreciated at the time. However, the tentative diagnosis can reasonably be made after reading Reimann's article and after considering the other cases in the above series. The four cases demonstrate that hyperproteinemia particularly occurs in those cases excreting slight amounts or no Bence-Jones protein. The finding of most widespread involvement of the bone marrow as in the three proved cases corresponds to the descriptions of other cases showing increased blood proteins.

The last two cases, which were diagnosed chronic nephritis, support the clinical observation of Bannick and Greene that multiple myeloma should always be considered in atypical cases of renal disease. Renal insufficiency was seen in the last three cases. In the two cases which came to autopsy it was unattended by any of the usual pathological findings in the common kidney lesions found in azotemia, or by the plugging of the tubules by casts as reported in those cases excreting much Bence-Jones protein. Precipitation of thick protein, as described by Bell in Case 3 was observed in the glomeruli in both of these cases (*2* and 3). However, the possibility of a functional plugging of the glomerular capillaries also by the clumps caused by intravascular hemagglutination must be considered. In Case 1 this phenomenon was plainly seen in the retinal veins when the circulation was slowed by firm pressure on the eyeball. The slowing up of the blood stream in the capillaries, plus the increased viscosity of the plasma due to glomerular filtration, might well favor a similar clumping in the glomeruli, as was seen in the eye of the only case of the series studied with the ophthalmoscope. Fahraeus reports that he believes rouleau formation occurs in the streaming blood, and that it can be demonstrated in cases showing a high sedimentation rate due to increased globulin or fibrinogen, by microscopy of the capillaries of the

nail bed or in the retinal vessels by the ophthalmoscope. He further states that intravascular aggregation of the red cells may be of even greater pathological importance in diseases than has been thought. He has shown by experiments with narrow glass capillary tubes, that a considerably greater pressure is necessary to force blood showing pronounced aggregations of erythrocytes through the tubes than normal blood.

The case of Wintrobe and Buell also presented symptoms which might well be explained on the basis of capillary obstruction. A peculiar mottling of the arms and lower limbs, blueness of the fingers, tips of the nose and the ears, and later coldness and blanching of the hands, feet, and even of the tongue occurred and finally bilateral thrombosis of the retinal vessels. For want of a better term the condition was diagnosed Raynaud's disease.

It is regretted that autopsy was not performed in Cases 2 and 3 before embalming, with the subsequent dilution of the blood by the fluid, thereby destroying histological evidence of intravascular hemagglutination; but it is hoped that cases in the future will be studied with this in mind.

Possibly changes in the osmotic pressure in the glomerular vessels may explain in part the retention of nitrogen, since the tendency for the blood with an increased oncotic pressure due to increased proteins is to hold electrolytes and absorb water from the tissues. Peters and Van Slyke [31] state that as the blood advances in its course to the capillaries (glomerular in the cases under discussion), the oncotic pressure increases due to concentration that has resulted from loss of blood water at the arterial end of the capillary, until it exceeds the hydrostatic (blood) pressure, and at the venous end of the capillary the flow of fluid is reversed, passing from the tissues into the blood. If the oncotic pressure in hyperproteinemia cases is increased, and as usual the blood pressure is low, it would seem reasonable to assume that there would be a decreased water output in the glomeruli, and consequent to this a diminution of excretion of nitrogen bodies.

The marked increase of uric acid in all the cases is no doubt due to the marked increase of purines from breakdown of nuclei in the tumor growths. The calcium increase is apparently due to the profound destruction of the bones. The parathyroids appeared to be not responsible for this phenomenon.

The abnormal bleeding in Cases 2 and 3 with the marked prolongation of both clotting and bleeding time in the presence of abundant fibrinogen, only slightly reduced (Case 3) or normal platelets (Case 2), and abundance of calcium is very difficult to explain. I have been unable to find similar instances in the literature.

The plasma cell growth in the spleen, liver, lymph nodes and kidneys of Case 2 without evidence of plasma cell leukemic changes in the blood is unusual, but similar findings are reported by Barr,[32] and several cases with much more bizarre pathological observations by Jackson, Parker and Bethea,[33] who believe the disease should be classed as a malignant lymphoma.

Summary

In four cases of multiple myeloma, profound autohemagglutination of the red cells occurred in dry and wet films, and difficulty in counting erythrocytes because of granule formation in the red counting pipette was encountered in two cases. Marked hyperproteinemia was proved to be present in three cases, was apparently present in the fourth, and seemed to be the cause of these abnormal phenomena. Renal insufficiency apparently resulted from plugging of the glomerular capillaries by inspissated protein and possibly by the clumping of erythrocytes or changes in osmotic pressure due to the increased protein. Intravascular clumping was demonstrated during life by the ophthalmoscopic examination of the retinal veins in one case when pressure sufficient to slow down the circulation was applied externally on the eyeball. Prolonged uncontrollable bleeding and clotting time and increased calcium content of the serum with little changes in platelet count occurred in two cases.

The findings of marked rouleau formation in the smears of two of the cases led to procedures finally making the diagnosis of multiple myeloma.

Multiple myeloma with resultant renal abnormalities should be suspected in cases of atypical nephritis.

BIBLIOGRAPHY

1. Reimann, H. A.: Hyperproteinemia as a cause of autohemagglutination; observations in case of myeloma, Jr. Am. Med. Assoc., 1932, xcix, 1411–1414.
2. Bönniger, M.: Ein seltener Blutbefund (Hyperproteinämie bei Myelomkrankheit), Deutsch. med. Wchnschr., 1933, lix, 770–771.
3. Freund, R., and Magnus-Levy, A.: Multiple Myelome; über Besonderheiten der Blutzusammensetzung, Ztschr. f. klin. Med., 1932, cxxi, 1–13.
4. Fahraeus, R.: Suspension stability of blood, Physiol. Rev., 1929, ix, 241–274.
5. Barker, L. F.: Discussion of nature and relationships of multiple myeloma with illustrative case, Med. Clin. N. Am., 1933, xvi, 1019–1027.
6. Perlzweig, W. A., Delrue, G., and Geschickter, C.: Hyperproteinemia associated with multiple myelomas, Jr. Am. Med. Assoc., 1928, xc, 755–757.
7. Bannick, E. G., and Greene, C. H.: Renal insufficiency associated with Bence-Jones proteinuria; report of 13 cases with note on changes in serum proteins, Arch. Int. Med., 1929, xliv, 486–501.
8. Shirer, J. W., Duncan, W., and Haden, R. L.: Hyperproteinemia due to Bence-Jones protein in myelomatosis, Arch. Int. Med., 1932, l, 829–835.
9. Wu, H.: New colorimetric method for determination of plasma proteins, Jr. Biol. Chem., 1922, li, 33–39.
10. Rowe, A. H.: The albumin and globulin content of human blood serum in health, syphilis, pneumonia, and certain other infections, with the bearing of globulin on the Wassermann reaction, Arch. Int. Med., 1916, xviii, 455–473.
11. Loeper, M., Forestier, J., and Tonnet, J.: L'hyperalbuminose paradoxale du sang des cancereux, Presse méd., 1921, xxix, 333.
12. Reiche, F.: Betrachtungen über die Senkungsgeschwindigkeit der Erythrocyten und über einen Fall von akuter calcipriver Osteopathie, Ztschr. f. klin. Med., 1931, cxix, 248–263.
13. Jacobson, V. C.: A case of multiple myeloma with chronic nephritis showing Bence-Jones protein in urine and blood serum, Jr. Urol., 1917, i, 167.

14. WINTROBE, M. M., and BUELL, M. V.: Hyperproteinemia associated with multiple myeloma, with report of case in which extraordinary hyperproteinemia was associated with thrombosis of retinal veins and symptoms suggesting Raynaud's disease, Bull. Johns Hopkins Hosp., 1933, lii, 156–165.
15. BENNHOLD, H.: Über die Vehikelfunktion der Serumeiweisskörper, Ergebn. der inn. Med. u. Kinderh., 1932, xlii, 273–375.
16. WEINBERG and SCHWARZ: Virchow's Arch. f. path. Anat., 1920, ccxxvii, 88.
17. CITRON, J.: Zur Symptomatologie der Myelome, Med. Klin., 1921, xvii, 808.
18. SHORT, J. J., and CRAWFORD, J. R.: Bence-Jones protein in blood serum leading to detection of multiple myelomatosis, Jr. Lab. and Clin. Med., 1931, xiv, 1092–1093.
19. MAINZER, F.: Bence-Jones'sche Proteinurie und Nierenfunction, Ztschr. f. klin. Med., 1932, cxix, 363–380.
20. ELLINGER, A.: Das Vorkommen des Bence-Jones'schen Körpers im Harn bei Tumoren des Knochenmarks und seine diagnostische Bedeutung, Deutsch. Arch. f. klin. Med., 1899, lxii, 255–278.
21. GABBE: Klinisch-wissenchaftl. Abend im Luitpoldkrankenhaus, Würzburg. Sitzung vom Nov. 1927, München. med. Wchnschr., 1927, lxxiv, 2224.
22. ZADEK, I., and LICHTENSTEIN, H.: Zur Klinik und Zytologie der multiplen Myelome, Folia haemat., 1931, xlv, 60–74.
23. ABDERHALDEN, E.: Ein Fall von Bence-Jones'scher Albuminurie, Ztschr. f. physiol. Chem., 1919, cv, 130–132.
24. HEWITT, L. F.: Urine proteins in nephrosis, pregnancy and myelomatosis, Lancet, 1929, i, 66–68.
25. D'ALLOCO, O.: Lavori d. Cong. di. Med. int., 1899, 258–266.
26. VON DECASTELLO, A.: Beiträge zur Kenntnis der Bence-Jones'schen Albuminurie, Ztschr. f. klin. Med., 1909, lxvii, 319–343.
27. DONETTI, E.: Riv. crit. di. clin. med., 1901, ii, 2789.
28. MARCOVICI, E.: Report of case of primary multiple myeloma with Bence-Jones protein in pleural effusion, ANN. INT. MED., 1929, ii, 881–911.
29. KARLINS, W. H., and LUNDQUIST, A. R.: Multiple myeloma; precipitation of Bence-Jones protein in blood, Minn. Med., 1933, xvi, 318–319.
30. BELL, E. T.: Renal lesions associated with multiple myeloma, Am. Jr. Path., 1933, ix, 393–420.
31. PETERS, J. P., and VAN SLYKE, D. D.: Quantitative clinical chemistry, 1931, i, 659, Williams and Wilkins Co., Baltimore.
32. BARR, D. P.: Multiple myeloma, ANN. INT. MED., 1928, i, 884–889.
33. JACKSON, H., JR., PARKER, F., JR., and BETHEA, J. M.: Studies of diseases of lymphoid and myeloid tissues; plasmatocytomata and their relation to multiple myelomata, Am. Jr. Med. Sci., 1931, clxxxi, 169–180.

THE TUBERCULOSIS OF CHILDHOOD *

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TUBERCULOSIS in childhood has many clinical manifestations. It can assume many forms which are seen predominantly in children and in addition many others seen in adult life. Only in recent years has its importance been realized, since the difficulties in diagnosis, and the insidious and occult forms in which it occurs have made it easily overlooked. There are many prevalent misconceptions about the disease, and several misleading pseudo-descriptive terms are imbedded in the terminology. Many writers on the subject are students of adult tuberculosis, pathologists or radiologists. This paper presents the point of view of the pediatrician, in the light of an active hospital service and the thorough pathological studies of Dr. Waldemar Grethmann.

Many physicians think that all children are infected, and that so-called " tuberculous infection " means little and may be disregarded unless " tuberculous disease " supervenes. This is a most dangerous view and often leads to neglect of children who deserve care. Those who hold this view entirely miss the value of a positive skin reaction. As a matter of fact, there can be no infection without disease since infection with the tubercle bacillus means that it has lived and grown in the body of its host and has set up its characteristic pathological lesions. No matter how small, how deeply seated, how obscure such lesions may be, they always carry the threat of serious results from dissemination. As Krause has said, " No tubercle is innocuous." (Figure 1.)

On the other hand many physicians do not realize that serious tuberculosis is not at all rare in infancy. Even in hospitals where every method of study is available the autopsy often surprises the clinician, and in private practice it is inevitable that the disease should be frequently overlooked. A health officer in a suburban county told me that not a single case of tuberculosis had been reported as a cause of death in over two years in his county. Yet the county sanatorium was full of adult cases. The diagnosis is not always easy, but is missed most often from failure to think of its possibility.

The terminology of the disease is full of confusion. Such a term as " childhood type of tuberculosis " is objectionable since it infers that children have only one form of the disease, i.e., the primary complex (primary focus plus regional lymph nodes). It is true that this stage is seen mostly in childhood, but is very often only a part of the story. Even very young children may show forms of the disease in various organs of the body, corresponding to those which we are accustomed to see mostly in adults. Moreover, the primary complex may occur later in life.

* Read at the Chicago meeting of the American College of Physicians, April 16, 1934.
From the Department of Pediatrics, New York University, and The Children's Medical Service and Pathological Laboratory of Bellevue Hospital.

"Masked juvenile" tuberculosis is a term used to describe the deep-seated, least manifest forms seen in later childhood. It is "masked" merely by the difficulties of diagnosis and is not a real form of the disease. Another term for these forms is "occult tuberculosis" as proposed by Engel. Still other terms such as "active" and "latent" disease are used with vary-

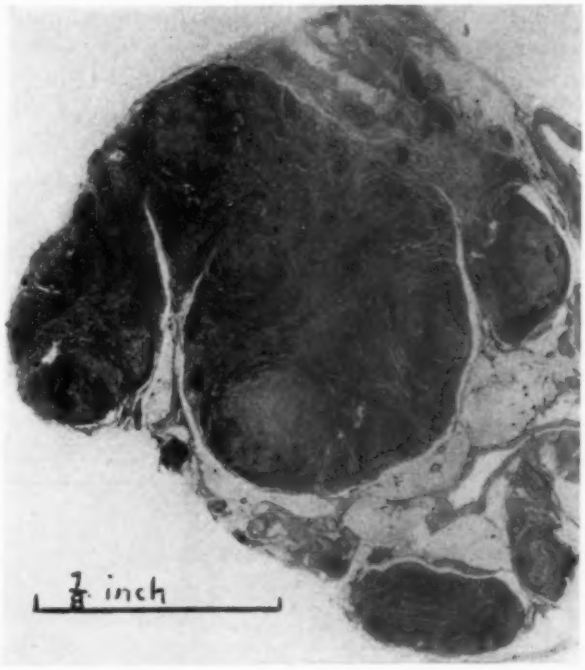

FIG. 1. Section of small lymph nodes taken from the neck of a child who died of tuberculous meningitis. The larger central node actually measured only 1/8 by 1/4 inch yet in it there were caseating tubercles and in the smallest node next it, was still another. These nodes are so small as not to be palpable through the skin yet contain caseous material capable of being disseminated and of setting up fatal disease. Yet such a child, before the advent of meningitis, would be considered by some an instance of mere "tuberculous infection."

ing meanings by different authors. Certain pathological terms used with loose meaning, i.e., "hilus tuberculosis," "epituberculosis," "miliary tuberculosis" (often used for disseminated pulmonary lesions of bronchopneumonic type) have further confused the general understanding of the disease.

An important point of contention is the relation of adult tuberculosis to that acquired in childhood. One school holds that adult disease is a reinfection from without or exogenous infection, in an individual whose immunity reactions have been altered by preceding disease. The proponents of the theory of endogenous infection believe that adult disease results from a dissemination which has occurred from a tuberculous focus acquired during childhood. The evidence is conflicting and many facts may be interpreted for either view. It is possible that both may be right. Both sides

agree, however, that tuberculosis in adults is probably most often seen in those who have been infected in childhood. Therefore a clear conception of the sequence of events taking place in the infected child is of prime importance for the understanding of tuberculosis.

Too often tuberculosis is thought of merely as isolated disease in one organ, i.e., the lung, a bone or joint, the meninges and so forth. In textbooks on pediatrics, medicine and surgery descriptions of clinical forms are scattered from cover to cover, and in only a few is any orderly description attempted. But the disease really goes on in a definite sequence from initial infection to the end, in much the same way as syphilis or other infections, though no complete parallelism should be drawn.

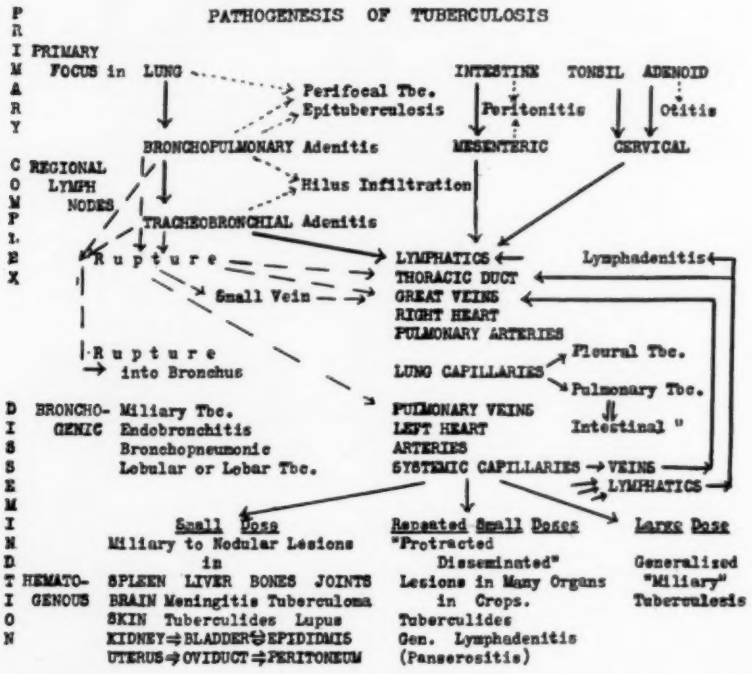

FIG. 2. PATHOGENESIS OF TUBERCULOSIS. In the above the solid arrows indicate transmission of bacilli through lymphatics or blood vessels, broken arrows rupture into vessels or air passages. The dotted lines show direct extension to adjacent structures. Double arrows through intestine or genito-urinary passages. Some probable pathways have been omitted to avoid too great complexity. Thus perifocal or bronchogenic tuberculosis may also infect the intestine secondarily.

Tuberculosis in childhood has been under study on the Children's Medical Service of Bellevue Hospital for the past 18 years. The material is peculiarly suited to obtaining an understanding of all the forms of tuberculosis occurring in childhood. Many patients are sent in from other hospitals as soon as the diagnosis is made, others are admitted for acute illness and are discovered to have tuberculosis. The large out-patient service picks up the forms of early and ambulatory disease. This combination of acute

and not acute material should be more instructive than that obtained from the tuberculosis clinics or sanatoria. There has been a large follow-up class, at first as an offspring of the original Nutrition Class. For over 10 years Dr. Edith Lincoln and her associates have had direct charge of all chest cases, both in the hospital wards and the chest clinic of the out-patient department. Much has been added to our information by this long continued follow-up and by the pathological studies of Dr. Grethmann.

Pathogenesis

A clear conception of its pathogenesis is necessary for any interpretation of the disease. It is a well known fact that in all tuberculosis there must be a primary focus. The bacilli are ingested, inhaled, or find lodgment on any part of the physiological surface of the body. There they set up their characteristic early inflammatory lesion. In various autopsy series the primary focus has been discovered in 90 to 95 per cent of cases showing tuberculosis.

Fig. 3. Primary complex in an infant. Primary focus shows as white spots (cut through at bottom of photograph (1)). Regional lymph nodes in hilus region. Note small size of primary focus with large lymphadenitis. (Prepared and photographed by W. Grethmann.)

The size of this, as of all tuberculous lesions, depends largely on the number of bacilli which initiate the process. The dosage of bacilli is thus an important factor. The primary focus is most often in the lung, usually in the

lower part of the upper or in the lower lobe, near the pleura. From the primary focus the bacilli are rapidly carried in the lymphatics to the regional lymph nodes, and there set up a tuberculous adenitis. The site of this, of course, depends on the site of the primary focus. In the lung the first nodes involved are the bronchopulmonary which lie in a chain along and close to the main bronchi. Bacilli passing through these are often filtered out in the tracheobronchial nodes about the bifurcation of the trachea and set up an

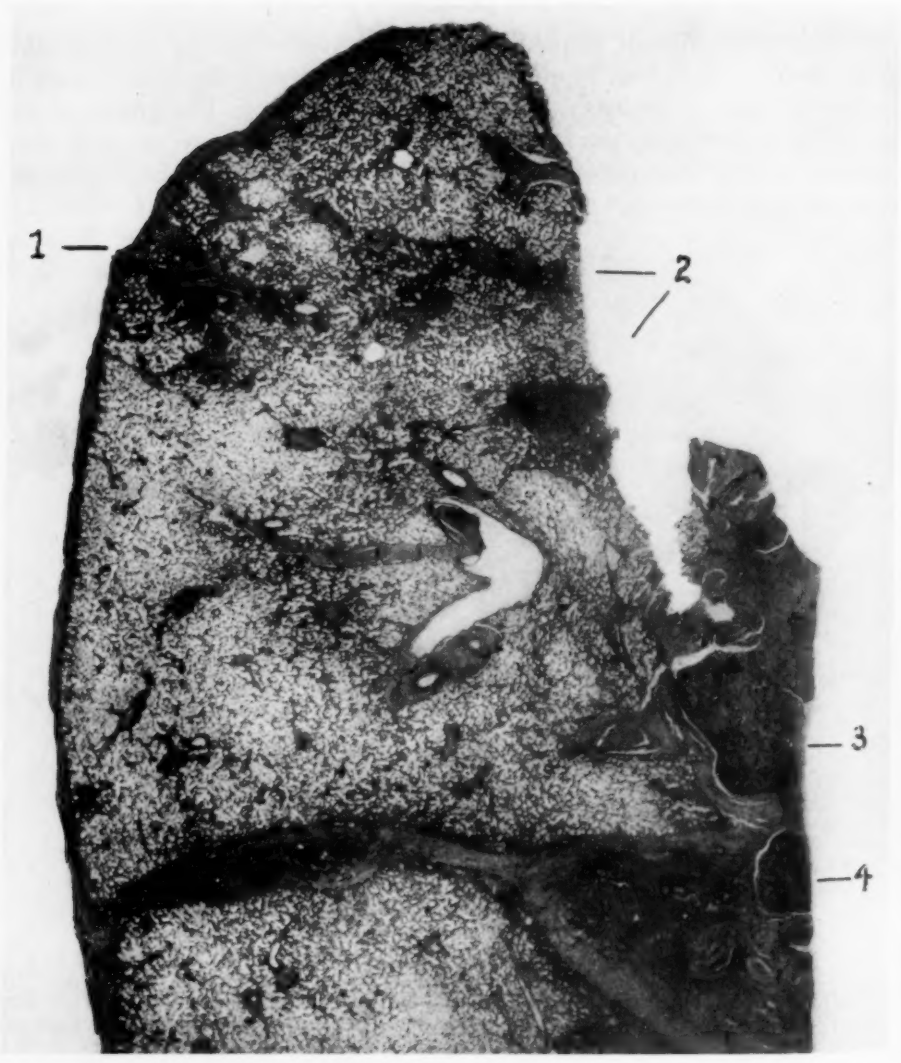

FIG. 4. Primary complex. Section of the right upper lobe of an infant dying from acute bronchopneumonia of lower lobes. This section accidentally cut through a primary focus (1) composed of several tubercles just under the pleura. It shows a few tubercles along the septa (2) and tuberculosis of a bronchopulmonary node (3). Just below this is a normal node (4). No bronchopneumonia shows in this section. This is a very early primary complex.

adenitis here or in the chains of paratracheal lymph nodes. The close proximity of these chains of nodes to the air passages and veins in the lung and mediastinum is of vital importance. (Figures 10 to 13.)

The combination of primary focus and regional lymph nodes makes up what Ranke has named the primary complex. It exists in every individual who has been infected with the tubercle bacillus. This is what is commonly called "childhood type of tuberculosis"—a clumsy and misleading phrase for the reasons given above. The primary complex merely represents the pathology of all first infections. When it occurs in infants and young children there is apt to be a larger adenitis than in cases acquired in later childhood, perhaps because the infant is often exposed more intimately and to larger doses of bacilli if he is exposed at all. (Figures 3 and 4.)

The primary complex may occur elsewhere than in the lung, though less commonly. A primary lesion in the intestine with mesenteric nodes, perhaps extension to the peritoneum, is second in frequency. The tonsil or adenoid with cervical nodes is the third. Extension to the middle ear occurs in rare instances. Other primary lesions in skin and mucous membranes are rarer.

The roentgen-ray findings give us a means of studying pathology even during life. In the primary complex there are no shadows in the majority

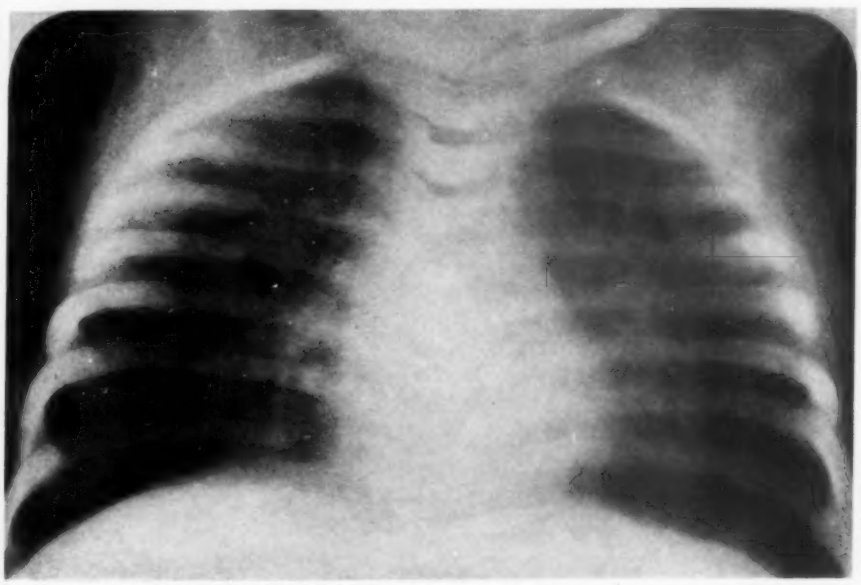

FIG. 5. Roentgen-ray showing definite enlargement of left hilus shadow due to tuberculous bronchopulmonary nodes in a small infant. No calcification. No trace of the primary focus is visible on the film although it was easily found at autopsy in the left upper lobe. The right hilus is within normal limits although larger and more mottled than the average normal. The mediastinal shadow is slightly widened.

of cases until calcification has begun. If the primary focus is larger than usual, one may occasionally see one or more small soft shadows in the outer

part of the pulmonary field but they are so inconspicuous as to be easily overlooked. In some cases where serial films are taken it is possible to recognize the site of the primary focus after calcification has taken place and then to pick out insignificant shadows in the earlier film in the same place. Early bronchopulmonary adenopathy may be seen as suspicious enlargements in the hilus region but can only be diagnosed with certainty when calcified or when very large. (Figures 5 and 6.) Tracheobronchial nodes widen the supracardiac shadow when very large, but considerable involvement may take place and be concealed behind the sternum. Lateral and oblique views are occasionally helpful, mainly when there is calcification.

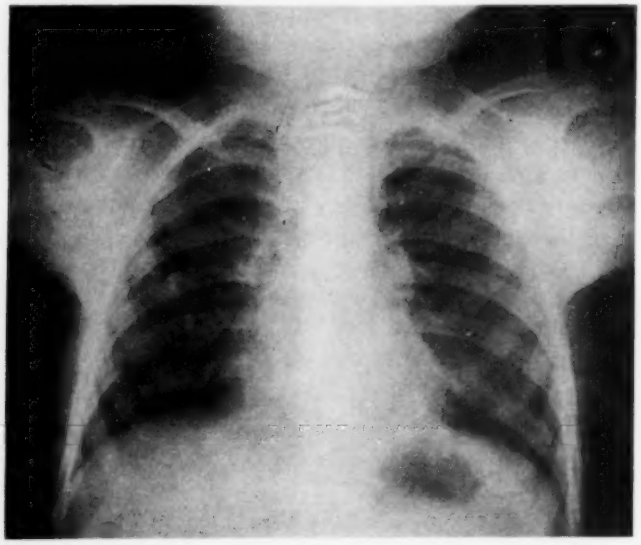

FIG. 6. Early calcification of primary focus over fifth right rib and bronchopulmonary nodes in hilus shadow. A film of the same child taken a year before showed a widening of the mediastinal shadow above the heart but no calcification.

The further course of the tuberculosis depends on several factors.

I. The course of each local inflammatory process.

II. *A.* Extension to adjacent structures.
To other lymph nodes.
To lung parenchyma.
B. Extension by rupture into an air passage, or bronchogenic dissemination.

III. Generalization or hematogenous dissemination.

I. The *course* of the inflammatory process may be stationary, retrogressive, or progressive. It must be remembered that tuberculous lesions, like all inflammatory processes, have the possibility of resolution and complete healing. Most individuals who acquire a primary complex overcome the infection and go for many years, or through life, with no subsequent symp-

toms. The primary focus and adenitis become resolved or encapsulated and calcified or even ossified. They then show as dense shadows on the roentgen-ray film for many years.

A tuberculous lesion may remain stationary for a certain period, neither retrogressing nor progressing. Such lesions may then go on in either direction. It is difficult to say just when we have this condition. Much so-called " latent tuberculosis " is found to be slowly progressive.

The lesion may become progressive and go on to caseation, but even then heal by encapsulation, fibrosis and calcification. Or softening and cavitation may take place with discharge of the contents into a viscus or through the skin, etc.

II. (*A*) *Extension to adjacent structures* may occur in any progressive lesion.

1. Extension from the lymph nodes to others may result in a general involvement of all the mediastinal nodes. This often gives enormous masses of tracheobronchial and paratracheal nodes. Even these may resolve slowly. On roentgen-ray they may be seen as a widening of the normal shadow above

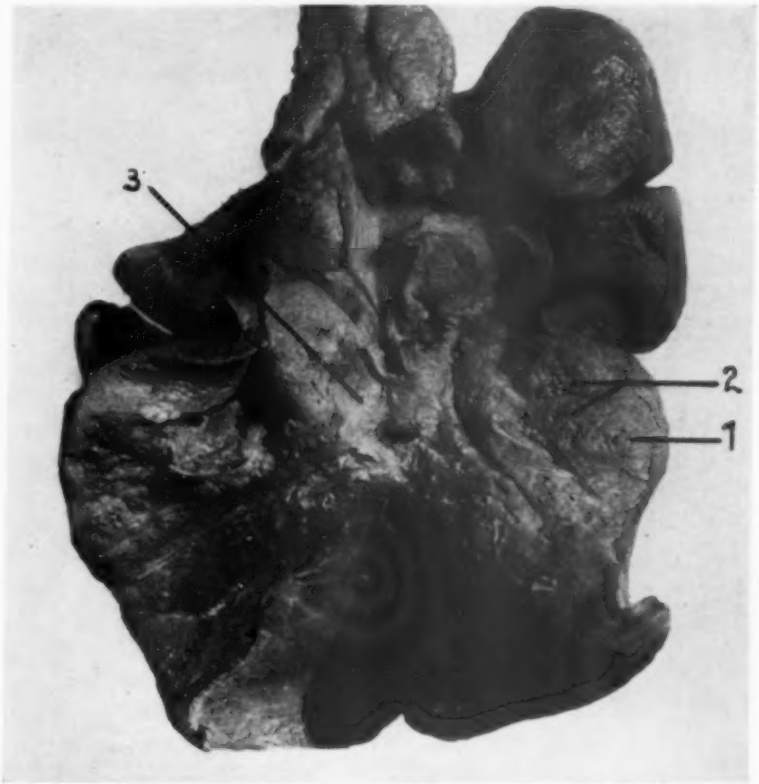

FIG. 7. Primary focus extending to adjacent lung. 1. Primary focus. 2. Direct extension from primary focus. 3. Bronchopulmonary nodes. (Prepared and photographed by W. Grethmann.)

the heart which is often mistaken for the thymus. These shadows are sometimes asymmetrical and at times have suggestive rounded outlines.

Pressure on a bronchus may occur, obstructing respiration in a lobe or whole lung. We have had cases of atelectasis resulting in chronic fibrosis with bronchiectasis caused by prolonged pressure of a tuberculous lymph node.

2. The primary focus occasionally increases in size, involves more and more lung tissue until real pulmonary tuberculosis results, giving a shadow on the roentgen-ray more or less like pneumonia. This has been called perifocal tuberculosis. (Figure 7.) This may resolve or go on to caseation and cavitation. In the latter case the caseous matter may discharge into a bronchus and be disseminated through the lung as described below.

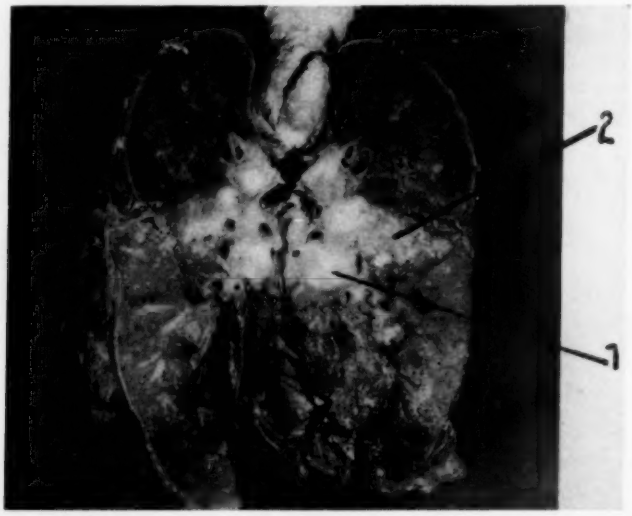

FIG. 8. Hilus infiltration. A true tuberculous infiltration (2) extending outward from a mass of caseous bronchopulmonary nodes (1). (Prepared and photographed by W. Grethmann.),

3. Extension from bronchopulmonary or tracheobronchial nodes may take place into the adjacent lung parenchyma. These are often wedge-shaped lesions with the apex outward, and are often benign, going on slowly to complete resolution. They may be seen to appear and gradually disappear in serial films leaving nothing except the calcifications of the original nodes. This is true hilus infiltration by a tuberculous exudative process. Some of these go on to caseation, however, and run the course of a caseous pneumonia, with bronchogenic extension, or walling off, fibrosis and calcification. (Figure 8.)

4. Epituberculosis is a term used by Eliasberg and others to describe cases in which massive lung shadows resembling pneumonia are seen, mostly in the upper lobes, which gradually disappear. The term was coined because it was believed that the shadows were not cast by true tuberculosis but by

simple inflammatory exudates around a tuberculous focus. The latter may be seen in many cases as a residual calcification after disappearance of the massive shadow. There are other possibilities explaining these shadows. They may be due to real tuberculous exudates which resolve in time, like those described above. Several of our autopsies on cases having shadows believed to be epituberculosis have shown definite tuberculous pneumonia. The third explanation is that there is pressure on a bronchus by an enlarged node, and behind it an atelectasis, or a lung filled with exudate analogous to the " drowned lung " described by Jackson in certain cases of foreign body in the bronchus. Bronchoscopy may reveal an obstructive pressure in some instances of epituberculosis. Whatever the exact pathology of this group, it is important to remember that massive shadows in the lung appearing after infection with tuberculosis do not always mean progressive caseous pneumonia, but at least a reasonable hope may be held out that complete recovery is quite possible. (Figure 9.)

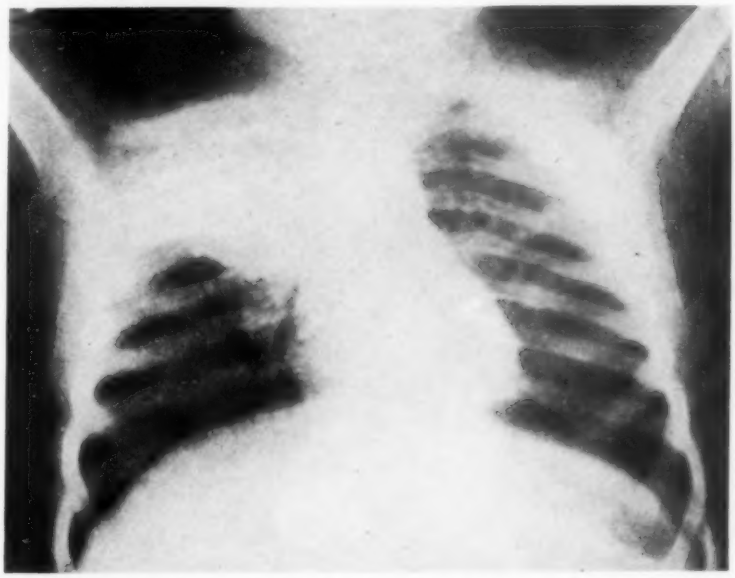

FIG. 9. Epituberculosis? The large shadow in the right upper lobe was thought to be a lobar pneumonia at first. But it persisted for two months and then gradually cleared leaving a dense calcified focus in the center. By some this is called " the evolution of the primary focus," but it seems more likely that it is a perifocal reaction, either a simple exudative process or the result of bronchial compression and atelectasis. Since calcification takes one or two years it is probable that the focus now calcified has been present before the massive shadow develops. In other cases we have been able to watch this sequence.

(*B*) *Bronchogenic dissemination* takes place when a caseous node or tuberculous cavity ruptures into an air passage. This is not an uncommon accident on account of the close apposition of the nodes to the trachea and bronchi. It is always a serious matter. The resulting lesions in the lung depend largely on the amount of caseous material inspired. Caseous ma-

terial and bacilli scattered through the lungs in small amounts cause scattered lesions of miliary size, or bronchogenic miliary tuberculosis. Larger amounts cause an endobronchitis or bronchopneumonia. Still larger amounts may cause a lobular or even a lobar pneumonic lesion. The seriousness of all these lesions is increased because they are on an open surface, ulcerative and progressive. They usually go on to chronic cavernous phthisis as seen in adults. (Figure 10.)

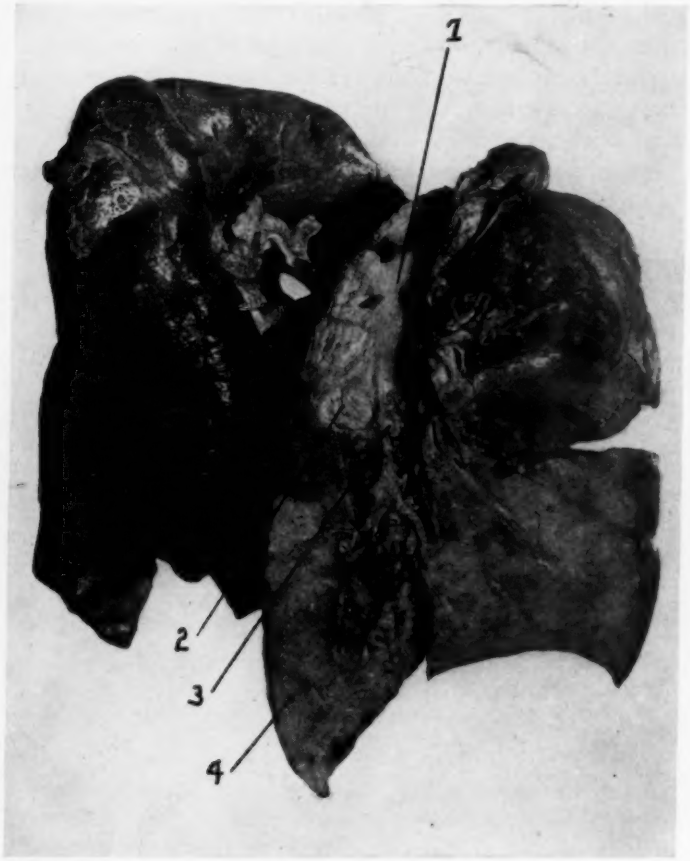

FIG. 10. Bronchogenic dissemination with lobar caseous pneumonia. 1. Lumen of large bronchus. 2. Caseous bronchopulmonary node. 3. Rupture into bronchus. 4. Caseous pneumonia of lower half of lung. In this case the caseous node had ruptured into the bronchus with a resulting aspiration of a large number of bacilli, giving caseous pneumonia of lobar extent. (Prepared and photographed by W. Grethmann.)

A proper roentgen-ray technic differentiates these just as in adult cases. Many times a bronchogenic dissemination is diagnosed as "miliary tuberculosis" from the film. To the most casual observer the lesions are not only of various sizes, but most of them are much larger than miliary. Lobular pneumonic tuberculosis gives larger mottled shadows and lobar tuberculosis massive shadows like lobar pneumonia. (Figures 11, 12 and 13.)

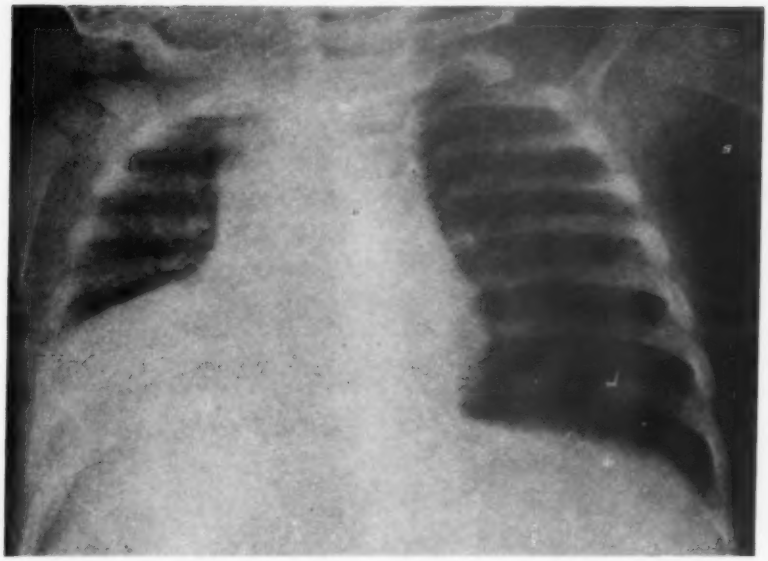

FIG. 11. Roentgen-ray of chest of colored infant. Physical signs of consolidation in right lower lobe, thought to be pneumonia? Note that heart and mediastinum are pushed to right probably by compensatory use of left lung, and perhaps by beginning obstruction of right main bronchus. Mediastinal shadow is wide, even allowing for displacement.

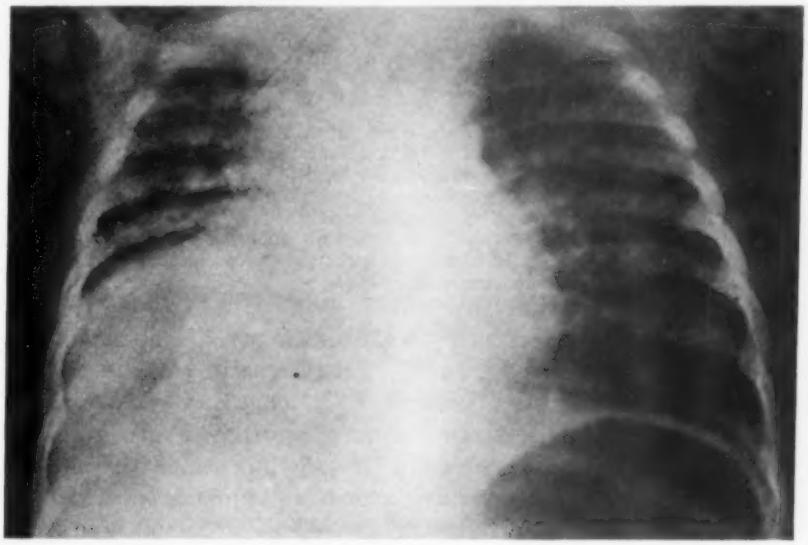

FIG. 12. Same patient as figure 11, two weeks later. Beginning cavitation in center of right lower lobe consolidation. Diffuse mottling of upper right and all of left pulmonic fields. This represents bronchogenic dissemination from discharge of cavity into air passages. Films of this kind are often read as "miliary tuberculosis." The shadows are too large and vary too much in size for this diagnosis.

Extension from bronchogenic tuberculosis may take place through the trachea and larynx to the gastrointestinal tract. The larynx is rarely involved in childhood. But the bacilli which are coughed up and swallowed

FIG. 13. Right lung of patient whose roentgen-rays are shown in figures 11 and 12. Lung is split from pleura to hilus and laid open. Note the caseous pneumonia of the lower lobe, probably from rupture of a lymph node into a bronchus. Cavitation in center. The upper lobe shows nodules of many sizes due to aspiration of the contents of the cavity. The left lung was like the right upper lobe. There was an enormous adenopathy of the tracheobronchial and paratracheal nodes. A fistula in ano showed tuberculosis and there was extensive involvement of the mesenteric nodes. There was tuberculosis in the liver, spleen and meninges, i.e., hematogenous dissemination.

may set up a tuberculous enteritis with mesenteric adenitis and a serious result. This is often missed entirely by the clinician, since diarrhea is not constant. Severe progressive emaciation is characteristic. Calcified abdominal lesions may sometimes be seen on the roentgen-ray film.

III. *Hematogenous dissemination or generalization.* This may begin early even during the development of a primary complex. Bacilli reach the blood stream in several ways. In the first place the lymph nodes are never perfect filters and bacilli pass through them to the lymphatics, thoracic duct and great veins. Or by rupture of caseous nodes into the thoracic duct, or a great vein, the same result is obtained. Furthermore, the presence of a small hemorrhage in one of the large caseous nodes often points out the site of a rupture into a smaller vein. Rupture into a pulmonary vein discharges bacilli directly into the greater circulation.

Bacilli reaching the veins of the systemic circulation are carried through the right heart and pulmonary arteries to the lung capillaries. They may find lodgment and set up lesions in the lung or in the pleura. This is one of the possible sources of pulmonary tuberculosis.

But the lungs are also imperfect filters and bacilli pass through them to the left heart and the larger circulation. They are then carried to various organs of the body where they may set up new lesions. The resulting lesions found depend on the doses of bacilli injected into the circulation, the lapse of time since the dissemination, and how often such dissemination has occurred. Three forms of hematogenous tuberculosis may be recognized.

1. A single small dose may lodge in any one organ or in several, and there set up lesions whose local course may be benign or serious, depending largely on the importance of the organ involved, and the further course of the process. Thus in brain, meninges, eye or kidney the result is usually serious, while in bone, liver and spleen it may be much less so.

The lung involvement may show in the roentgen-ray as soft shadows of miliary or small nodular size. They are often found at the apices or in the upper part of the lungs. They may calcify later. In adolescent children they are called " Simon foci " since Simon first described them. There is still discussion as to whether these lesions may be the method of development of adult apical tuberculosis.

2. A single large dose gives a generalized tuberculosis with lesions of equal size all over the body, often called " general miliary tuberculosis." But " miliary " again refers to the size of the lesions and this generalized form often has lesions of nodular size if many bacilli lodge in one site. The roentgen-ray films of the lung show many small soft shadows of about the same size and in varying numbers. They may be few and, at first, so small as to be invisible, but become apparent as they enlarge with time. It is possible for these lesions to be present in the lung for a long time since the tubercles are not on the surface as in bronchogenic dissemination and so are less apt to ulcerate. They may even heal.

3. Repeated doses of varying amounts give lesions of different sizes and different ages. They are found in various organs, the lungs, the kidneys, the liver and especially the spleen, where they appear as the so-called " large nodular spleen tuberculosis." Besides these various parenchymatous lesions there is usually present a tuberculous lymphangitis and lymphadenitis of groups of lymph nodes in various parts of the body. In this form of hematogenous tuberculosis we may also find an extensive involvement of the various serosal surfaces. With each dose of dissemination a crop of tuberculides may appear in the skin. The pathological picture of this form of hematogenous tuberculosis was first pointed out by Schuermann of Hamburg, who coined the term " protrahierte Durchseuchung." This may be best, but not quite accurately, translated as protracted dissemination. Dr. Grethmann deserves credit for having elaborated as a clinical entity this form of hematogenous tuberculosis which is not uncommon but which ap-

parently is not generally known. He has collected a series of about 70 cases of this form in individuals of different ages, which will be published in the near future. After seeing some of his autopsies we have been able to determine this form of tuberculosis in a number of children, from the repeated new lesions, crops of skin tuberculides, varying sized shadows in the lungs, calcified nodules in the spleen, general adenopathy and sometimes panserositis.

In involvement of the genito-urinary tract, transmission is usually from the kidney to the bladder and thence to epididymis. But a lesion in the latter may appear first and extend to the bladder and prostate also.

It must be repeated that the further course of any lesion set up by any of these means of dissemination may be progressive or stationary or retrogressive. The character of these secondary lesions is altered by the change in the body reactions due to the previous injection into the system from the primary infection of the products of the growth of the tubercle bacilli and by the resistance of the host.

From the foregoing, which is based on numerous cases under each pathological entity described, it is obvious that tuberculosis is found in children in many forms besides the usual one supposed to be characteristic—"the childhood type." A failure to keep in mind the inevitable sequence of events leads to all sorts of illogical classifications in which the primary focus and then the lung lesions are described in detail, and later the tracheobronchial adenitis. Such a divorce of the two elements of the primary complex is unnatural and confusing. In some books general miliary tuberculosis is described first among the clinical forms.

Incidence

The incidence of tuberculosis in childhood depends largely on the amount of exposure to open adult cases, that is to the amount of adult disease active in the community. Hence it is more common in cities, in the crowded slums, and more in European cities than in this country. It is much less prevalent in the better classes of society, in smaller towns and in most rural populations. Exposure to an open case in the family or to a servant is the usual source of infection. The disease, in this country, is nearly always of the human type.

There are two measures of the incidence, namely the tuberculin skin reaction, and the death rate. There is a widespread impression among physicians that the tuberculin reaction is of little significance, and that practically all children after infancy are infected and give a positive reaction. This is far from the truth. The tuberculin reaction gives us very definite information as to whether a given child has been infected or not. A positive skin test shows that the tubercle bacillus has lived and grown in the child's body and has given off the substance we know as tuberculin, exciting a sensitivity of the body cells to further contact with tuberculin. It must be remembered that a positive tuberculin skin test does not tell whether the

disease is active or not, nor whether the lesion in which we are interested is tuberculous, but merely that the individual has been infected at some past time.

Of the skin tests, the Mantoux or intracutaneous test has supplanted all others, since it is much more reliable than the Pirquet, Moro, or Calmette tests. It is generally used today in all pediatric services. The initial dose is usually 1/20 to 1/10 milligram (1/20 to 1/10 c.c. of 1 : 1000 dilution) except in cases where massive or very active disease is suspected, where 1/100 mg. is safer. If the first test is negative it should be repeated with increasing dosage in all doubtful cases, using 1/5, 1/2 or even 1 mg. A different area should be used for each test since it is possible to sensitize local areas of the skin by reinjection. When a test has been definitely positive it should not be repeated for several months since the second reaction may be severe, especially if done on the same arm. The main sources of error are the use of inert or contaminated solutions, improper technic of injection, the presence of fever from intercurrent disease, or lowering of skin sensitivity by overwhelming tuberculosis. In the latter instance it may take 2 to 10 mg. to excite a reaction, and since these patients are often moribund, they may die before the dosage can be increased sufficiently to give a positive test.

Care should be taken not to excite a generalized febrile reaction by too large an initial dose. This should never exceed 1/10 mg. The local reaction is occasionally severe, even vesicular and occasionally necrotic, but this is rare and with proper forethought in giving small initial doses, should not discourage the use of the test.

Many series have been published showing the incidence of positive reactions in various parts of the world. Unfortunately the early series from Vienna and other European cities showed a very high incidence, up to 50 per cent at 7 and 95 per cent at 12 years. These figures were accepted as representing the prevalence of tuberculous infection everywhere. It is certain that they are much too high for the cities of this country, even in the population of the slums. Figure 14 shows the incidence curves in various series. The Bellevue statistics (the New York curve) have been recently compared with series from other hospitals in New York by Grolet and the curves are almost identical. They correspond closely to statistics from Minneapolis, Ontario, San Francisco and other parts of this country. In these series about 10 per cent of living children give positive reactions in the first two years, 15 per cent in the third and fourth years, 20 per cent at five to seven, 30 per cent at seven to nine, and only about 40 per cent at ten to twelve. Since all children are not infected the skin test becomes most important.

The death rate from tuberculosis is another measure of incidence. The death rate is high in the first two years, as high as any year until early adult life. It falls off rapidly up to five and the lowest rate is from five to 15, after which there is a steady rise. In other words tuberculosis is often a

fatal disease in infants, but relatively not fatal in school children. Moreover the death rate in infancy is undoubtedly much higher than statistics indicate, since many fatal cases are overlooked if no autopsy is performed. The diagnosis is obscure in infants and many deaths are attributed to marasmus or bronchopneumonia which are in fact due to tuberculosis. Yet

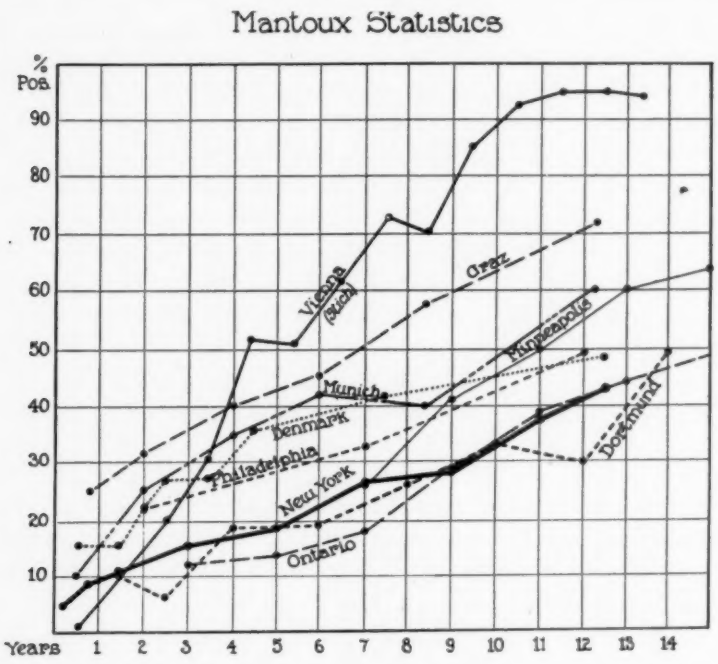

FIG. 14. Curves showing incidence of positive tuberculin reactions in different parts of the world. Note that in nearly all cities the incidence does not exceed 50 per cent at 12 to 14 years. (Reprinted from "Tuberculin Skin Reactions" by Charles Hendee Smith, Am. Jr. Dis. Child., 1929, xxxviii, 1137.)

tuberculosis is not always fatal in infancy. It must be noted that while about 10 per cent of infants give a positive skin reaction, the total death rate is never as high as 10 per cent of the infant or child population at any age from tuberculosis, or indeed, from all causes. Therefore many must recover. Children infected after the first two years have a relatively good chance of handling the disease unless meningitis occurs.

The question is often asked as to whether it is better for the individual to be infected early or not. It is believed by some that an early infection gives a certain immunity to later serious disease. This may be true, since it has been found that nurses going into a sanatorium are less likely to acquire active tuberculosis if they have a positive skin test. On the other hand the child who is infected early is much more likely to have massive or progressive disease with fatal dissemination or meningitis than is the one infected somewhat later. It is certainly undesirable to have young children

infected. Therefore they should be kept from contact with open cases of tuberculosis.

The Calmette (B.C.G.) inoculation with living attenuated bacilli is done with the idea of giving the infant a relative immunity during the years when he is most susceptible. The intracutaneous method is the best; the oral administration unreliable. The tuberculin reaction becomes positive, but after some years is said to become negative again. Since this seldom occurs in tuberculosis acquired in the ordinary way, it brings out the thought that the latter is rarely completely cured. The B.C.G. inoculation is still under trial. Many feel that it is unjustifiable and dangerous, and time alone will tell whether the death rate is influenced sufficiently to justify its wide use among infants living with open cases. Some of the early reports have been hopeful.

Clinical Varieties

The clinical aspects of tuberculosis are different in infants (up to two or three) and in older children, and they need separate consideration.

Tuberculosis in Infancy

In infancy the primary focus gives few symptoms, no physical signs and no roentgen-ray shadow until it becomes calcified. A transient unexplained fever and perhaps failure to gain well are its only symptoms. The lymphadenitis gives no signs at first nor until the nodes are quite large. No suspicion of the disease may be aroused until enormous adenopathy, or bronchogenic or hematogenous dissemination has occurred, or until there is some serious or fatal complication such as meningitis. In fact the element of surprise is the predominant note in nearly all infantile tuberculosis.

The most common symptom complexes are the following:

1. Tracheobronchial adenopathy of large extent. Such infants usually have fever and do not gain well. The chest shows practically no signs, though occasionally parasternal dullness or an increase in the area of tracheal breath sounds may be noted. The roentgen-ray gives a wide supracardiac shadow, often rounded outlines on one side or both, suggesting nodes. Such shadows are often diagnosed as enlarged thymus. In the older infants the primary focus is occasionally calcified and there may be beginning calcification in the hilus region (bronchopulmonary nodes). There may be pressure obstruction of a bronchus with absent breath sounds over a lobe or a whole lung. With rest and care some children, even with masses large enough to cause obstruction, improve greatly and go on to slow recovery. The greatest danger is from rupture into a bronchus. (Figure 17.)

2. Cases of "marasmus." Small infants are admitted to the hospital with marked emaciation with or without irregular fever. There may have been a story of feeding difficulty, but many infants have done well at first and then have begun to fail. Routine roentgen-ray should be done on all such patients and may reveal definite tuberculosis in the lymph nodes or wide

dissemination, or even large cavities. This group usually has a bad prognosis.

3. Cases simulating pneumonia. Infants are admitted with relatively short histories,—fever, prostration, cough and physical signs of consolidation or with crackling, resonant râles at the bases suggesting bronchopneumonia. These infants may be emaciated but are often fairly well nourished. The roentgen-ray shows mottled shadows over part or all of the pulmonic fields, indicating bronchogenic disseminated tuberculosis or localized consolidation much like a lobar pneumonia. In the latter instance only the long course, or beginning cavitation, or the finding of bacilli in the sputum makes the diagnosis. It is exceptional to have recovery in this type, although it may be impossible at first to differentiate a given case from those described as epituberculous. (Figures 11, 12 and 13.)

4. Unexplained high fever, without local signs, often turns out to be disseminated pulmonary or generalized tuberculosis.

5. A final group includes the cases which are definitely suspected of tuberculosis from the outset.

Tuberculous meningitis stands first in this group in frequency and seriousness. This is seen as a terminal event in widespread tuberculosis or it may be the first clinical manifestation. An infant who has been in apparently perfect condition suddenly becomes ill, with vomiting and fever, and irritability. Nervous symptoms soon appear, somnolence and coma, paralyses and so forth. Infants often lack the irritative signs seen in older children, such as stiff neck, positive Kernig and Brudzinsky signs, and are entirely flaccid with absent reflexes. There is a rising leukocyte count. The spinal fluid shows high protein, low sugar, mononuclear cells and bacilli.

Bone disease in infants is more common in the small bones of the hands and feet than in the larger bones. Dactylitis is often apparently destructive but may heal with rest and minimal surgical treatment leaving an almost normal bone. (Figure 15.)

Disease in other organs in infants is difficult to diagnose clinically. Liver and spleen tuberculosis give no symptoms, though the organs may be definitely enlarged. Kidney tuberculosis is seen much less often than in older children.

In the protracted disseminated form various organs may be affected. Thus a child of 18 months admitted to Bellevue with fever and a fresh crop of tuberculides was found to have one radius, the opposite ulna and four metacarpal bones affected, as well as a massive shadow in one lung. Yet his nutritional state was not bad. Repeated crops of new lesions may occur in the skin and other organs. One case showed calcification of nodules of different sizes in the spleen on roentgen-ray. The prognosis is not altogether unfavorable depending somewhat on the number and size of the crops of new lesions, and the site of the main involvement; but it is in general

unfavorable. This form will be discussed more fully in forthcoming papers by Lincoln and Grethmann from this service.

Physical examination of the lungs is often most unsatisfactory in small children. The stethoscope is the least useful instrument at our disposal in

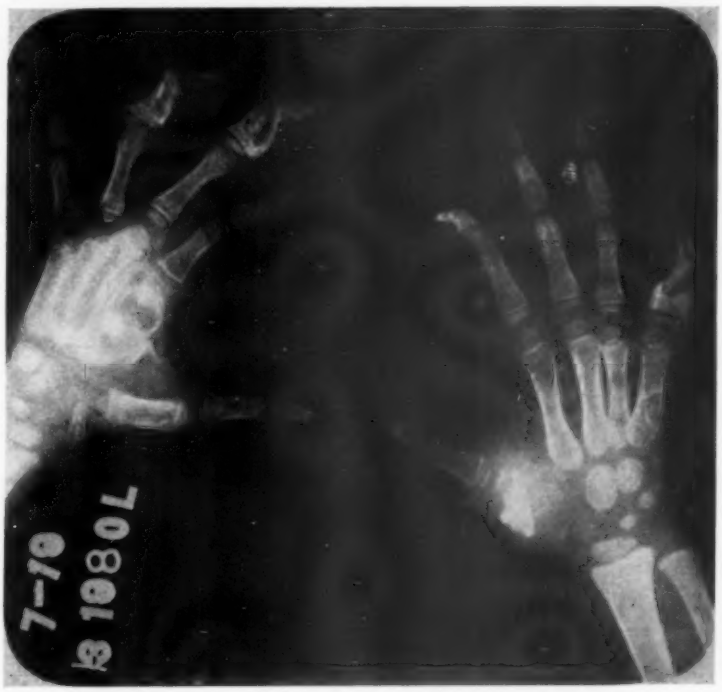

FIG. 15. Dactylitis of the bones of the hands of an infant with generalized tuberculosis.

the tuberculosis seen in childhood. The roentgen-ray may reveal large lesions in cases where no signs whatever can be elicited either before or after seeing the film. Even massive consolidation or large cavities may be completely missed by the most careful examiner. Inconstant râles, more or less resonant (crackling) are often the only signs heard. At times definite signs of consolidation are made out in pneumonic tuberculosis or in "epituberculosis." Hilus infiltration even of large extent, is usually silent since it is surrounded by normal lung. The need for the lightest percussion must be emphasized in examining all infants.

Blood. In all the acute and exudative forms of tuberculosis there is a leukocytosis. It is often incorrectly believed that this disease gives a leukopenia, and an attempt is made to exclude tuberculosis when an increased leukocyte count is found. Even tuberculous meningitis has a slowly rising leukocyte count. The monocytes are increased in all active tuberculosis, but the difficulty of the technic makes the monocyte count a research rather than a clinical method.

Tuberculosis in Older Children

If all older children who have been infected, as shown by a positive skin test, are thoroughly studied it will be found that they fall into the following groups.

1. Recent infections in those who have been infected within two years or less, that is those who have a fresh primary complex. These comprise approximately 15 to 20 per cent of the reactors, as determined by the slope of the curve of positive tests. If calcification requires one and a half to two years the children infected less than that time show little on roentgen-ray, unless there is large adenopathy and this is less common than in infants. Some of these children may have a primary complex so insignificant as to give no symptoms, others may show real symptoms of activity during the acute stage.

2. A certain number will show calcification in the hilus region of the lung, perhaps a calcified primary focus in the parenchyma. But this group is not as large as would be expected. Barnard, Amberson and Loew found only 20 per cent of positive roentgenograms in a group of 1000 of high school age, reacting to tuberculin. We should expect the percentage to be less in younger children. Certainly many cases are seen in which no calcification nor signs of previous lung involvement remain. Of the children with calcifications some may have healed all their lesions, but others may still have active tuberculosis. The presence of calcification on a film does not mean complete healing.

3. Children who have been infected more than two years who have healed their lesions by resolution and show no calcification. They should be symptom free if healed. It is probable that some of the cases having symptoms of activity have lesions not demonstrable by our present methods.

4. A few have definite pulmonary tuberculosis. This is not a large group and does not tend to increase in size with age, because pulmonary tuberculosis in children is a serious and fatal disease, much less likely to become arrested than in adults. The older the child, the more does the disease approach that seen in adults.

5. A few have non-pulmonary tuberculosis in mesenteric nodes, cervical nodes, bones, kidneys or skin, etc.

The matter of importance is to try to make out whether the disease is active or not, since this is the keynote of treatment. Constitutional symptoms are more significant than roentgen-ray findings or physical signs. The child is too often forgotten in the study of his roentgen-ray shadows.

Nearly all the studies of tuberculosis in childhood have been based on roentgen-ray films. But if only 20 per cent of those infected are roentgenologically positive, and if many of these may have active lesions, the roentgen-ray as a diagnostic screen is not valid in picking out active cases. This has been shown again and again in surveys in which a large number of children have been roentgen-rayed and the positive cases then tested with tuberculin. This is not only a most extravagant method of selection, but a

most inaccurate one. The better way is to test the children first, then roentgen-ray the positive reactors *and in addition seek for signs of activity in all, regardless of the roentgen-ray findings.*

The clinical picture of activity is characteristic and quite obvious to a trained observer. The symptoms and signs are few but added together should be enough to arouse suspicion of what is happening to the child.

Fever is an almost constant sign of activity: that is, a rectal temperature which rises above 100° nearly every day. Temperatures under 100° may be disregarded in childhood. The fever is irregular, rising to a different level on different days, and not always at its height in the afternoon. The highest point may be at any time of day or even in the middle of the night. The great irregularity is characteristic.

Failure to gain weight at the proper rate, and as a result more or less malnutrition, is always a suspicious sign. No other disease seems to exercise so prompt an effect on the nutrition in childhood. Gain in weight may occur in adults with advancing lesions, but is rarely seen in children. There is often secondary anemia.

FIG. 16. Aspect of child of two years with active tuberculosis as shown by fever. Note the miserable, anxious expression. This child never smiled.

Languor, easy fatiguability, anorexia and irritability are all probably more or less due to the fever. These children act and look languid, unin-

terested in life. Some of the younger ones have a facies which is peculiar and suggestive of serious disease. The eyes look large, dreamy, or absent-minded, often lustrous. The child does not smile, nor can he be made to do so by any of the usual tricks of doctors or nurses. The lips appear to be thickened or pouting. This is perhaps a disuse phenomenon, since smiling is a regularly recurring matter in normal children. Such children may remain in this condition for months with complete apathy, never smiling once. Many have a fretful expression, or one of anxiety, as if they could forsee the shadow of their impending fate. This facies is seen mostly in children between two and four years. It is not constant in all active cases, but may be the first thing to call attention to the diagnosis. (Figures 16 and 17.)

FIG. 17. W. H. Aspect of a boy of two and one-half years, weight 19 pounds. He had long lashes, lustrous eyes, thick lips and unsmiling expression seen in many younger children with active disease. He had pressure on the left main bronchus from an enormous mass of tracheobronchial nodes causing absent breath sounds over the whole lung, with irregular fever. Nevertheless in three months he had gained six pounds, had no fever, good breath sounds in the left lung and was a merry, normal looking child.

Other corroborative signs are seen but are inconstant.

Hypertrichosis, or increased hair on the body, especially on the nape, arms and legs, with long lashes. Increase in hair is seen also in many chronic infections, such as prolonged surgical suppuration. A familial tendency to hairiness must be discounted. The present custom of having

children wear bathing suits or sun suits much of the summer certainly seems to stimulate the growth of hair on arms and legs in some children. Nevertheless, long lashes and hairy arms and nape are often seen in children with tuberculosis which is, or has recently been active, and it is a suggestive finding.

Phlyctenules on the cornea are nearly always due to the toxins of tuberculosis. The photophobia and aspect are characteristic and may be the first suspicious signs.

Tuberculides are also significant, especially the papulonecrotic tuberculide because it represents a definite hematogenous spread. These occur on the trunk and extensor surfaces of the extremities. They are small raised lesions with a depressed necrotic center and are mistaken for chicken pox at times. They often occur in crops at long intervals.

FIG. 18. J. G., 11 years. In apparently perfect health until skin eruption appeared. On the extensor surfaces of the forearms are numerous papulo-necrotic tuberculides. She had slight fever at times up to 100.5°. Roentgen-ray negative. No other foci discoverable. The Mantoux reaction to 1/10 mg. was nearly three inches in diameter. This case probably represents a small discharge of bacilli into the blood stream from a mediastinal node. All the discoverable localization at this time was in the skin.

Erythema nodosum should probably be classified as a toxic tuberculide. It was formerly thought to be rheumatic, and is still reported as a common occurrence in some studies of rheumatism. It is much more often seen in

children with tuberculosis than in our large rheumatism and cardiac clinics. The tuberculin skin test is rarely negative. In one case, an attack of erythema nodosum was apparently precipitated by a Mantoux test. The appearance of the acutely red swellings on the shins is so suggestive of periostitis that the children are often sent in to the surgical wards. The tenderness is much less than would be expected from the appearance. It may be the first thing to call attention to tuberculosis, as in the case of a small girl who was recently admitted for erythema nodosum which had suddenly come on while she was in apparently perfect health. Her roentgen-ray showed a marked primary focus with beginning calcification and definite bronchopulmonary nodes in the hilus. She had irregular fever which had never been suspected. Her small brother also was found to have a primary complex. In this case the erythema nodosum was a fortunate incident for both since it led to early diagnosis.

It is obvious that this symptom complex in the older children is indefinite. Irregular fever, languor, failure to gain properly make up the triad of sig-

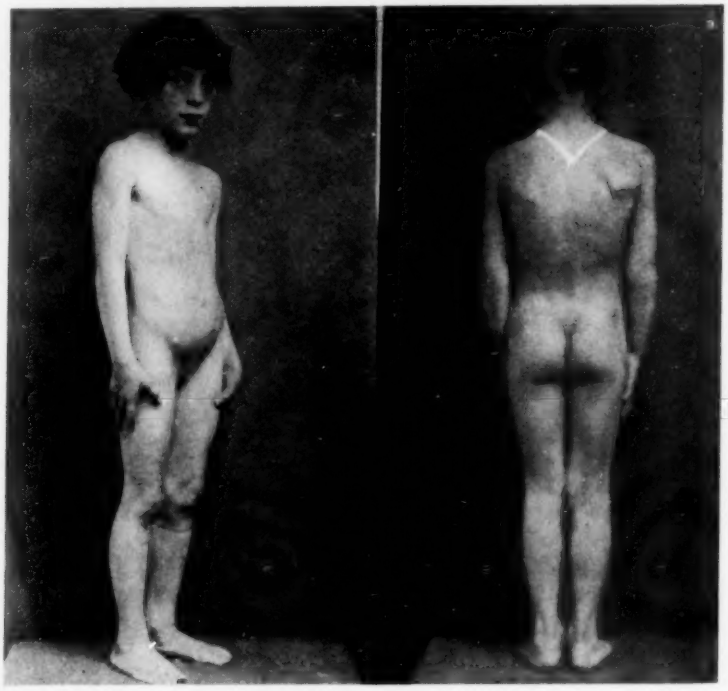

FIG. 19. J. B., 6 years. Mother brought her to out-patient department complaining that child was tired all the time, sitting around the house and eating little. She had lost some weight. The child was fairly nourished but had lustrous eyes, long lashes and a hairy nape. Her temperature was 100.5° by rectum. Tracheal whisper to fifth dorsal spine area indicated by white line. No abnormal signs in the lungs. The Mantoux was positive to 1/10 mg. The roentgen-ray showed a calcifying primary focus at the right base and calcification in the right hilus region. This is an example of the indefiniteness of the symptoms seen in these cases and how easily the diagnosis may be overlooked. It is even more easy to overlook active tuberculosis when the roentgen-ray is entirely negative.

nificance with or without hypertrichosis, and should always lead to further study. A Mantoux test, if positive, should be followed up by roentgen-ray study. Phlyctenules and tuberculides are more definitely diagnostic.

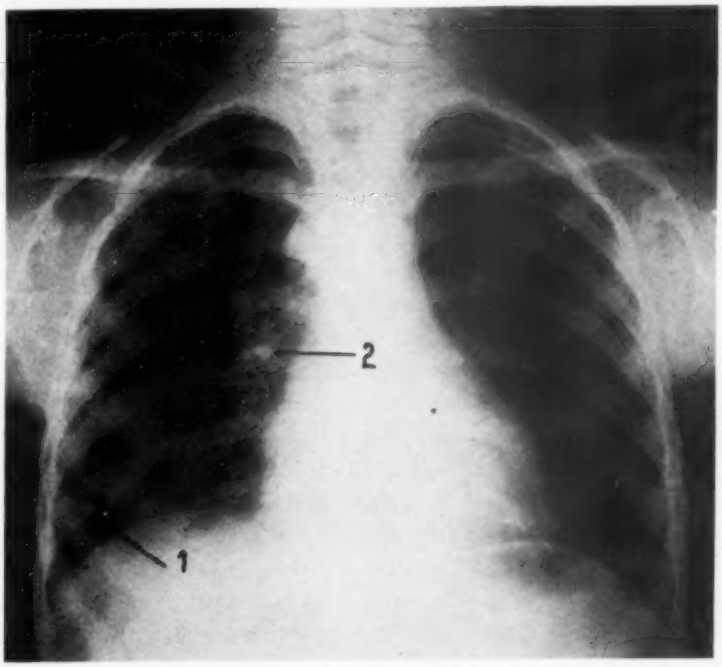

FIG. 20. Roentgen-ray of J. B., described under figure 19. 1. Calcified primary focus. 2. Calcified bronchopulmonary nodes. Note that child still had fever and apathy, although calcification had begun.

In many cases the roentgen-ray will show little, perhaps some calcification. It may be pointed out that too much is often read into slight variations in the size and shape of the hilus shadow by many radiologists. There is considerable variation in the shape and density of these in normal children. Only large variations or definite calcification may be considered pathological. The tracheobronchial nodes are not often large enough in older children to encroach on the pulmonic fields. Small lesions may be found in the lungs, occasionally hilus infiltration. Pleural effusion is more common in older children than in infants.

Stomach washings have demonstrated tubercle bacilli, by guinea pig inoculation, in a small number of children thought to have only lymph node tuberculosis, showing that, even when there are no symptoms, small open lesions in the lungs may be present which are not recognized by roentgen-ray or physical examination.

In children approaching puberty definite apical infiltrations like those in adults are occasionally found. Children may develop definite advancing fibrocaseous phthisis exactly like that of adults. They have then the cough,

expectoration, wasting and fever, as well as the characteristic roentgen-ray findings. Care should be exercised, however, not to confuse with this type of disease the cases of non-tuberculous fibrosis with bronchiectasia more frequently seen in childhood.

Physical examination of the chest reveals nothing as a rule, nor should physical signs of the usual kind be expected except in the frank pulmonary cases. There is one sign whose value is not generally appreciated—that is the one bearing the name of D'Espine. A good deal has been written about it, but still very few medical schools teach its technic and significance. It is usually dismissed in a word as being of no importance.

D'Espine's sign deals with the transmission of the whispered voice, or the whispered concomitant heard after the spoken voice in the interscapular region. I have found the whisper more satisfactory, since the concomitant may not be present at all in a given child. The sign is elicited as follows. When a child whispers " three," or " three trees " and one listens over the cervical spinous processes a definite whisper of tracheal quality is heard. Over the lower dorsal spines the usual vesicular whisper is obtained. If the stethoscope is moved up and down it is found that there is usually a sharp line at which the transition from tracheal to vesicular whisper takes place. This line is V-shaped as a rule, the apex being at the first to third dorsal spines and thence running up and out over the root of the neck to about mid clavicle. The child should stand with the head slightly bent forward so that the cervical and dorsal spines make an even curve. D'Espine thought that any whisper or whisper concomitant below the first dorsal was abnormal and the sign has been called " positive " when below this level. Others have found that it might be as low as the third dorsal or even the fourth in normal children, so that it is better to note the exact level of tracheal whisper transmission than to use the term positive or negative.

The sign is based on the increased transmission of the whisper from the trachea to the spinal column in all cases where there is increased density of the structures in the mediastinum. Thus there is a lowered tracheal whisper transmission in mediastinal adenopathy, tuberculous or simple, in Hodgkin's disease, leukemia, pneumonia, fibrosis or tuberculosis of the lung and in spinal deformities when there is an abnormal relationship between the trachea and the spinal column.

I have used this sign on all children I have examined since 1912 when Stoll first called it to my attention. In a small series in 1921 I reported a correlation between the D'Espine and positive tuberculin reaction which seemed more than accidental. Since that time my impression of the value of this sign has been strengthened. It is not pathognomonic of tuberculosis of the mediastinal nodes. Still it is a definite physical sign which should be given the consideration of any physical sign, no more, no less. In the absence of any other causes of enlargement of the nodes, or of any cause for increasing the density of the neighboring lung, a tracheal whisper trans-

mitted below the third or fourth dorsal spine is almost certain to be associated with a positive tuberculin reaction.

Percussion of the interscapular region may give a lowered upper level of pulmonary resonance, i.e., the relative dullness normally found at the apex which extends down to about the spine of the scapula, may extend lower than this if there is increased density of underlying structure. Increased significance may be attached to a lowered change in percussion note if it is associated with a low tracheal whisper, especially if both are asymmetrical. But one must not expect to discover small lesions by percussion through the spinal column and thick muscles of the back.

It is not possible or necessary to go into the clinical aspects of bone, joint or genito-urinary, skin, eye and other forms of localized tuberculosis. It is proper, however, to point out the too common mistake of making a diagnosis of tuberculosis on clinical signs alone, or even on the roentgen-ray film without so simple a procedure as the tuberculin test. I have seen this done repeatedly by general practitioners, by internists high in their branch of medicine, and by various specialists in orthopedics. Since the skin test is of smaller use in adult work, it is very easy to forget its value in children.

Diagnosis

In infancy, fever, loss of weight, with or without persistent signs in the lung, should suggest tuberculosis. Of course, bone disease and meningitis always do so. A Mantoux test, the roentgen-ray and carefully recorded temperature and weight curves are necessary to complete the diagnosis.

In older children, failure to gain, languor, fatiguability, a low transmission of the tracheal whisper and hypertrichosis are suggestive. Phlyctenules, tuberculides or any local disease may be the first sign indicating the need of fuller study by a careful rectal temperature curve, Mantoux and roentgen-ray. With a positive Mantoux, fever is significant of activity even with a normal roentgen-ray.

In the diagnosis of tuberculosis three questions should always be kept in mind.

First. Has the child been infected with tuberculosis? The answer to this is easily obtained from a properly performed Mantoux test.

Second. What is the site of the disease? The answer may be given by the symptoms, a careful physical examination and good roentgen-ray films. All of these may be practically negative. But in this event we feel sure that the mediastinal nodes are probably the site of the disease, since they are involved in most primary infections, or secondarily to some degree even when the primary complex is elsewhere.

Third. Is the disease active, stationary, or cured? This must be judged by general symptoms, fever, the effect on the nutrition and, of course, by any signs or symptoms of local activity if they are present.

Treatment

The treatment of children with tuberculosis is based on the same principles as those used in adults. If there are no local or general signs of activity a child should lead a normal life with somewhat closer watching than usual. Activity of the process as shown by fever, failure to gain or local signs of activity demands rest until all the symptoms have entirely disappeared. A rest cure on a veranda, on a roof, or in an open room should be planned with exact attention to every item in the entire day.

The diet is important and should be prescribed with care. Children do not take food nor digest it well if fed too often. Milk between meals or with meat meals is not advisable for any child. It is better to give the three simple meals which a child usually takes with bread and butter between meals. This digests and leaves the stomach in two hours and puts weight on the child better than too much milk, which stays in the stomach three to three and a half hours. The popular slogan that every child needs a quart of milk to drink every day is not based on experience with normal children and hence should not be the rule with sick ones. If a child has 10 or 12 ounces of milk at breakfast and supper and gets some cooked in his soups, desserts, and so forth, he actually receives the greater part of a quart. But if he takes too much milk he is likely to refuse other foods and so get into the habit of eating an unbalanced diet. Cod liver oil should be given for its effect on the calcium metabolism and perhaps for the protection against respiratory infections. It should be given after meals, in any form the child takes best, plain, in orange juice, in emulsion or with a malt preparation. The numerous substitutes, viosterol, tablets, concentrates, etc., which are popular today, do not replace cod liver oil. Some of them may do harm from the large amounts of vitamin D contained. There is no evidence that it is desirable to give enormous amounts of this substance. The same warning holds against over-use of the ultra-violet ray.

No food should be forced, and the child should not be coaxed, amused or bribed to eat. A meal should be put before him and nothing said about it. In half an hour it should be taken away and nothing given until the next feeding, no matter what has been left. In a few days he will eat willingly.

The above is closely linked with a psychological aspect of the care of chronically sick children which must never be forgotten. Some children develop a " lime light complex " very easily and will try in every way to get attention. Under the circumstances it is very easy for a distracted mother, who has been told that her child has tuberculosis, to spoil him at any cost, fearing that he may not recover and wishing to make him happy. But spoiling never makes a child happy for long and unless a reasonable discipline is maintained it is impossible to carry out any planned régime. It is easily possible to keep any child perfectly happy for any number of years on a

complete rest cure if all this is understood at the outset and if he is never allowed to become sorry for himself. One of the essentials is a good bed table which fits across his lap on which he can play, with enough simple toys or easy lessons to keep him occupied. Without occupation no child will stay at rest.

In a planned rest cure in childhood forethought must be taken about the bowels. As a rule a mild laxative such as aromatic extract of cascara may be needed, at first at least. It should be gradually lessened in amount and an attempt made to induce a movement with high residue foods, agar, mineral oil, and so forth. If the bowels do not move adequately after breakfast, a small soapsuds enema should be given at once so that the habit of a normal time for evacuation shall be maintained.

The difficult period comes when a child first begins to get up. As soon as the temperature stays under 100° for several weeks, if he is up to normal weight, and if there is no contraindication from local signs of activity, he may be allowed up a little at a time, but with care to avoid over-exercise. The effect on the temperature is the guide, as in adults. Unfortunately it is necessary to put him back to bed again and start over again if the temperature again rises as a result of activity.

Pneumothorax is much less useful in children than in adults. When a real parenchymatous lesion develops it is too often steadily progressive and dissemination through bronchi or the blood stream is frequent and serious. On the other hand the earlier stages are most amenable to treatment. As stated above, the primary complex heals and may not ever be recognized in the great majority of infected children. When an early stage is recognized through the examination of contacts, by a tuberculin test, or a roentgen-ray, or from an early tuberculide, etc., the family is to be congratulated, since these children do very well indeed if properly treated. Under good care it is rare to have serious progressive dissemination or meningitis. Even in cases of serious local lesions in bone, kidney, etc., the ability to recover completely is unbelievable. Some children who are febrile, emaciated, and who look as if they were doomed, will make a surprising and complete recovery under good care. Mention has been made of the possibility of resolution of lung lesions which cast massive shadows.

The resistance of the child, his race, economic status, and so forth, all influence the prognosis. Negroes and Puerto Ricans do badly in New York. The ability of the parents to plan and carry on a long campaign for months or perhaps years is one of the most important factors.

Conclusions

A clear knowledge of the pathogenesis of the forms of tuberculosis occurring in childhood must be kept constantly in mind when studying infected children, since they have many forms of the disease besides the primary complex.

All children are not infected and therefore the tuberculin test is a most valuable diagnostic aid.

The effect of the disease on the temperature and weight curves more often suggests the diagnosis than local signs of disease in the lung.

The roentgen-ray often makes a surprising diagnosis but may show very little or nothing in a child with definite constitutional symptoms.

Tuberculosis is a serious disease in infants but even they usually recover from primary complex and often from secondary lesions. Older children do very well when properly handled, if the diagnosis is made early, before meningeal or serious pulmonary involvement.

Since nearly all tuberculosis begins in childhood a further reduction in the death rate can probably best be effected by better understanding of the disease in children.

HEMOCHROMATOSIS: REVIEW OF THE LITERATURE AND REPORT OF THREE CASES *

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HEMOCHROMATOSIS, as the name indicates, is a metabolic disorder characterized by the deposition of the blood pigments hemofuscin and hemosiderin in various organs and tissues, associated with progressive interstitial fibrosis and sclerosis of the organs subjected to the abnormal deposition of pigment, particularly the liver, pancreas and spleen.

In a large proportion of cases (85 per cent according to an analysis of 53 cases by Blanton and Healy [4]) the disease is accompanied, especially in its later stages, by diabetes mellitus. Most patients show a definite increase in pigmentation of the skin, due to hemosiderin and often associated with increase in melanin.

Troisier, in 1871, first described a "bronze cachexia" occurring in diabetes, and 10 years later Hanot and Chaufford [15] called attention to a condition which they termed "bronzed diabetes." It is undoubtedly true that these diseases were the same as that described and named "hemochromatosis" by von Recklinghausen [37] in 1899.

Incidence. Hemochromatosis, also known as pigmentary cirrhosis, is said to be comparatively rare, and only a few more than 100 cases have been reported in the literature. It occurs almost exclusively in males, less than half a dozen females having been reported. Nearly all cases fall within the middle-age group.

In the clinical records of over 100,000 admissions to the Johns Hopkins Hospital, Futcher found but three instances of hemochromatosis. In 1435 autopsies at the University of Kansas Hospital,[20] only three cases of this disease were found, whereas at the Bellevue Hospital,[4] New York City, only four cases of hemochromatosis were noted in 5000 autopsies. Mallory, Parker and Nye [22] found hemosiderin deposits only four times in 224 cases of cirrhosis of the liver.

There have been about as many cases reported in Europe as in America, and the disease has been observed in Australia and New Zealand. Cheney [7] describes a case occurring in a Japanese male, 35 years old, only three cases in Japanese having been reported in the literature.

Etiology. The cause of the abnormal deposition of iron is not known. Alcoholism and chronic copper poisoning may be of etiological importance, although Cheney,[7] Critchlow,[9] and others reported cases with no history of exposure to these possible factors. It is quite possible that such conditions may exist without being elicited in obtaining the history.

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Rous and Oliver [30] caused hemochromatosis in animals by repeated blood transfusions, but there is no conclusive evidence of abnormal blood destruction in men. Mallory, Parker and Nye [22] produced the disease in animals by feeding copper, and their experiments were later confirmed by Hall and Butt.[14] The latter produced pigment cirrhosis in rabbits, sheep, and to a lesser extent in white rats, resembling closely the early manifestations of hemochromatosis in man, by feeding these animals copper acetate. Moreover they found that alcohol administered in conjunction with the copper acetate not only failed to hasten or augment the production of pigment cirrhosis, but also reduced materially the storage of copper in the liver in both rabbits and white rats. They conclude that hemofuscin, which is produced in the livers of rabbits treated with copper, contains iron in a masked form. These workers found hemosiderin in the livers of the copper fed rabbits in much smaller quantity than hemofuscin and they believe the former to be derived from the latter.

Sources of copper poisoning which must be considered in discussing the etiology of hemochromatosis include the following:

(1) Distilled liquors contaminated with copper dissolved from the copper worm of the condenser, by action of organic volatile acids.
(2) Occupations involving exposure to copper dust, such as work in brass foundries and mills, copper and brass fabricating mills, telephone line repairing, etc.
(3) Probably also acid foods, jellies, candies, etc., contaminated by copper vessels used in canning them, particularly if their reactions are strongly acid.

In 1929 Funk and St. Clair [13] reported a case of hemochromatosis without diabetes and they conclude it is unlikely that increased hemolysis is the cause of the iron pigmentation. These investigators believe that the rôle played by copper is secondary to an unknown etiologic agent. They furthermore raise the question as to whether other heavy metals such as zinc, manganese, and nickel might not also be retained in the tissues, as well as iron and copper.

Some authorities, notably Sheldon,[33] feel that the time taken for these deposits to accumulate is very long, and it is possible that the disease is an inborn error in metabolism, the accumulation being so slow that the characteristic clinical symptoms do not appear until middle age is reached.

Hemochromatosis occurring in a woman is reported by Hartman.[16] His patient was 28 years old and had had allergic symptoms (eczema of the face, and intolerance for milk and eggs). She gave a history of unusual sensitivity to cold and susceptibility to respiratory tract infections, including frequent attacks of sinusitis. Another case of hemochromatosis in an allergic patient was reported by Constam.[8] His patient was a male, 58 years of age, with a history of bronchial asthma of 25 years' duration.

Howard and Stevens [18] conclude that the disease may depend on some

injury to the liver resulting in hepatitis, and this in turn leads to a disturbance of the iron metabolism, so that there is a slight and prolonged retention of the iron, both exogenous and endogenous.

Older writers have considered hemochromatosis a form of diabetes. We know now that pigmentary cirrhosis is one of the rarer *causes* of diabetes, and is not a *form* of diabetes. Hemochromatosis exists, in a minority of cases, with normal urinary and blood sugar findings.

Pathology. The striking postmortem feature is the bronze color of the liver, pancreas, and other organs and tissues, especially after fixing in alcohol. The bronze or chocolate discoloration is due to the deposition of the blood pigments, hemofuscin and hemosiderin, the latter being an iron containing derivative of hemoglobin. Chemically, hemosiderin is an iron albuminate in which iron is held in relatively loose combination. Several writers have noted increased amounts of copper in organs, Mallory [22] reporting 10 such cases.

Tedstrom [36] reasons that since the iron deposits are increased in the cells normally metabolizing iron, it would seem that the initial lesion is a failure of the organs which normally take care of the products of blood destruction to do so.

Donaldson [10] is inclined to believe that the primary lesion is one of damage to liver cells by an unknown toxin or toxins. This finds expression in the gradual disappearance of the liver cells, and in the production of fibrosis. In addition to those changes which characterize cirrhosis in general, the damaged liver cells are in some way affected so that the cells in question are no longer capable of dealing with iron offered to them in the normal course of events. This iron, therefore, probably derived mainly from the food, slowly accumulates in the damaged liver cells, where it gradually undergoes chemico-physical changes which result in the final appearance within the cells of coarse masses of iron pigment. This accumulation is analogous to what happens in case of fatty infiltration of the liver.

As regards the pigment in places other than the liver, Donaldson suggests that the massive deposits in the retroperitoneal glands consist of granules transferred there from the liver or other organs, and that the pigmentation in other organs, chiefly in secretory cells, varies in amount and extent of distribution in different cases and is probably dependent in some way on the degree of interference with the metabolism of iron in the liver. Hemofuscin is also present in most instances, but this derivative of hemoglobin does not contain iron in any recognizable form.

Callender [5] believes that accompanying these pigments and as a result of their deposit, sclerotic lesions are produced in the liver and pancreas. He concludes that the accumulation of pigment in the liver cells leads to their destruction and replacement by proliferation of the periportal connective tissue, thus giving rise to cirrhosis of the liver. In a similar manner, cells of the pancreas and other involved organs are destroyed and replaced.

Diabetes mellitus is found to exist in the majority of cases of hemo-

chromatosis, but is absent in some. When the pigmentary cirrhosis involves the pancreas to such a degree as to impair the function of the islets of Langerhans, diabetes mellitus is added to the picture.

Increased pigmentation of the skin is not always present, but is found in most cases. It is thought to be dependent more on interference with adrenal function than on deposits of iron in the skin, although both undoubtedly play a part. A severe degree of adrenal impairment may produce a picture which suggests Addison's disease, just as the pancreatic lesions may result in diabetes.

Sheldon,[33] reporting his study of a moderately advanced case of hemochromatosis that came to autopsy, found excessive deposits of iron in all tissues examined, except the blood, which contained slightly less than the normal amount. This seems to indicate that the essential feature of this metabolic disorder is an increased avidity of the tissues for iron, which slowly accumulates in the cells in a form which they are incapable of excreting. He believes the pigment originates in the cells and is not carried to them by the blood stream from the liver and other places where it is present in exceptional amounts. He found that the central nervous system had nearly three times the normal amount of iron, but this excess was not demonstrable by the ordinary staining methods. It is believed that in cases in which large excesses of iron are demonstrated in the central nervous system by the usual staining methods, the deposits represent a later stage of the same process.

In Sheldon's case, as in one of the cases here reported, the pituitary gland was definitely involved. In his case abundant pigment was noted particularly in the anterior lobe, where it was almost entirely intracellular. It was exceptionally pronounced in the large oxyphilic cells. The pigment tended to occur around the margin of the cells rather than around the nucleus. Pituitary pigmentation was also noted by Wilson and Weiser.[38]

In health, the body contains about three grams of iron, but in advanced cases of hemochromatosis the liver alone has been found to contain as high as 38 grams. Yet, with all this accumulation of iron-containing blood pigment, there is no evidence of abnormal blood destruction in most cases. Anemia is sometimes present, especially in the late stages, but it is not a prominent feature, and is usually attributable to some complicating condition. One of the cases here presented showed aplastic bone marrow at autopsy, and the progressive anemia developing toward the end of the disease was apparently attributable to defective hematopoiesis rather than to increased blood destruction.

Symptoms, Course and Prognosis. General weakness, malnutrition and gastrointestinal disturbances are frequent complaints. Blanton and Healy,[4] in their analysis of 53 cases, noted that ascites occurred in about one-third of the patients and that glycosuria was present at some time in 85 per cent of cases. In 61 per cent of patients the spleen was not palpable. The skin pigmentation attracted attention in only about half of the cases.

The symptoms of cirrhosis of the liver, usually hypertrophic, or of diabetes, may be the first indications of ill health. Moeller and Hutton [27] report in detail a case occurring in a woman 53 years old, and lay emphasis on the extreme sensitivity to cold displayed by this patient during the course of her disease. She was not diabetic and had no clinically demonstrable cirrhosis of the liver.

The disease usually develops insidiously and the course is protracted. When diabetes does occur, it is a feature of the later stages. Krall and Ginsberg [20] found the average duration of life after glycosuria is discovered to be one year.

Critchlow's [9] patient had a bronzed skin for many years, and finally sought hospitalization with symptoms of severe diabetes without acidosis. The blood sugar on admission was 400 mg. Insulin was given in doses of 15 units a day. In three days the blood sugar was reduced to 200 mg., and still there was no acidosis. The abdominal distention and ascites increased, however, and he died a non-diabetic death on the twelfth day.

Esmonde Smith [34] reports a rapidly progressive case of hemochromatosis with diabetes. The symptoms were of only two weeks' duration. The skin had a leaden hue, but the patient's relatives had noticed no change in his color prior to onset of his symptoms. This patient had apparently been in excellent health and was employed up until two weeks before his death. Such rapidly fulminating cases are exceptional, however, and one feels impelled to assume that the underlying disorder is slow in its development. In most instances, the disease is chronic and slowly progressive to a fatal termination.

Diagnosis. Pigmentation of the skin, hepatic cirrhosis and diabetes mellitus are considered the diagnostic triad of hemochromatosis. Where such a combination of clinical findings exists recognition should not be difficult, but because of the rarity of this metabolic entity, clinicians are apt to overlook one or two of the triad components and label a case either cirrhosis of the liver, or diabetes mellitus. Furthermore, the skin pigmentation is not always apparent, nor is diabetes a constant or necessary feature of the disorder. The author believes that the most important diagnostic clue is the color of the skin, as the three cases here reported were suspected because of their peculiar complexion.

The skin has been variously described as dark brown, leaden, blue-black, and grayish-brown. It is usually a brownish slate color, not typical of the pigmentation of Addison's disease, nor is it the grayish slate color of argyria, but a shade somewhere between the two. In none of the three cases here described, with the possible exception of the fatal case, was the skin discoloration very pronounced, yet the odd, sallow complexion suggested the correct diagnosis during life. The diagnosis is firmly established by repeatedly finding hemosiderin in the urine, or by the presence of hemosiderin in an excised piece of skin.

The apparent difficulty of clinical recognition is indicated by the statement of Mills [26] that in 17 pathologically advanced cases, only two were recognized during life and the diagnosis proved by the demonstration of hemosiderin in an excised piece of skin.

Cheney's [7] case, occurring in a Japanese, did not have diabetes and curiously enough, despite his racial color the diagnosis was suggested by pigmentary changes in the skin.

Addison's disease, argyria, and diseases producing jaundice must be considered in the differential diagnosis. The latter conditions are at times baffling, as jaundice not infrequently accompanies the cirrhosis of hemochromatosis and leads one to overlook the concomitant pigmentation of the skin which is due to the abnormal deposition of melanin, hemofuscin and hemosiderin.

Treatment. As chronic overindulgence in alcohol is an accepted etiologic factor, prophylaxis should include avoidance of alcoholic excess. A similar warning to avoid possible copper poisoning may be wisely heeded. The treatment of the disease, largely symptomatic, is the treatment of hepatic cirrhosis and if present, of diabetes. Regarding the latter the usual therapeutic measures may require modification and caution in administration.

Callender [5] invites attention to the fact that in these cases of "bronzed diabetes" insulin should be used with extreme care, as the protective glycogenic activity of the liver cannot be depended upon to mobilize glycogen normally. Rapid and extreme reductions in blood sugar may thus result from the use of insulin and give rise to serious symptoms.

The diabetic phase of Critchlow's [9] case responded satisfactorily to small doses of insulin, 15 units a day, but his patient died of hepatic insufficiency 12 days after admission to a hospital. On the other hand Constam's [8] patient, having reached a diabetic stage, was remarkably refractory to insulin. Instead of being susceptible to hypoglycemic reactions, this patient required as high as 300 units in one day to reduce the hyperglycemia. It would be interesting to ascertain whether this man was refractory to insulin only when in a state of acidosis, or whether large doses were continually ineffective.

Moeller reports a case in a woman showing no diabetes and no clinically demonstrable liver cirrhosis. She obtained distinct benefit from the following medication: pituitary (ant. lobe) 2 grains, suprarenal (whole gland) 1 grain, strychnia 1/60 grain. Capsules containing this mixture were ingested three times a day. Two years later, when her case history was published, she was still maintaining her improvement.

Case Reports

Three cases of hemochromatosis were observed on the Medical Service of Walter Reed General Hospital within the last 12 months. The patients

underwent thorough survey in hospital, but only significant or pertinent findings are herewith abstracted from their clinical records.*

Case I

A white male bachelor, aged 52, retired army officer, was admitted to Walter Reed General Hospital May 25, 1932. His family history was negative.

Personal History: He admitted moderate indulgence in alcoholic liquors until two years ago. His history included the usual childhood diseases and also scarlet fever with left otitis media and subsequent faulty hearing and occasional slight aural discharge. He had had pneumonia as a child and again in 1899, mild typhoid fever in 1898, mild dengue fever twice, herniotomy in 1917, tonsillectomy in 1920 and again in 1929, appendectomy in 1930.

Present Illness: His complaint on admission was of pain in metacarpal-phalangeal joints of middle and index fingers of the right hand, a condition which had bothered him for the past 13 years and for which he had undergone repeated treatment and surveys for focal infection. When operated upon for acute appendicitis in 1930 an enlarged liver was found and believed to represent Hanot's cirrhosis. This patient has since noted that his color is "pasty" and that he has gradually developed a discoloration of the skin of the lower half of both legs, without swelling. For many years his skin has been dry and lusterless, especially on the extensor surfaces of limbs. He has a tendency to sleep a good deal and is somewhat drowsy during the day. There has been long standing loss of libido and potentia.

Physical Examination: The patient was a fairly well muscled and nourished male, 66 inches tall and weighed 125 pounds (five pounds under his usual weight). The skin was dry, slightly thickened and doughy, and complexion muddy. There was a grayish-brown pigmentation of the skin of the lower half of each leg. Slight varicosities of the veins of the lower extremities, but no edema. The blood pressure was 138/78. The testicles were atrophic, liver enlarged and firm, four fingers' breadth beneath costal margin, not tender; spleen palpable; some pain on extreme motion of metacarpal-phalangeal joints of index and middle fingers, right hand. Physical examination was otherwise essentially negative.

Roentgen-Ray Examinations: Slight narrowing of interphalangeal joint spaces of both hands was noted. Stereoscopic plates of the skull showed the sella to be small and apparently completely closed. The gastrointestinal series revealed no organic abnormality, although the lowest point of the greater gastric curvature in the upright position was on a level with the anterior superior interspinous line. The first portion of the duodenum while diminutive and somewhat spastic shows no constant defect. There was a small calculus, 5 cm. in diameter, in the gall-bladder.

Laboratory Findings: Six urinalyses were negative except for trace of albumin in one specimen. Concentration test indicated mild renal impairment, but the phenolsulphonephthalein test showed elimination of 75 per cent of the dye in two hours. Urine negative for hemosiderin. Examination and culture of feces showed no blood, parasites, ova, or *Streptococcus hemolyticus* or *viridans*, but a small green-producing coccus and a larger gram-positive coccus were isolated, and an autogenous vaccine prepared. The differential blood picture was normal. The red blood cell count was 4,000,000–4,130,000; white blood cells 5,500–6,500; Hgb. per cent, 65–75; polymorphonuclear neutrophiles 50–54 per cent. Wassermann and Kahn tests were

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The photomicrographs were made at the Army Medical Museum. Acknowledgment is made to Major Virgil Cornell and to Major Raymond Dart of the Army Medical Museum, for their further study and illustration of the pathologic material in these cases.

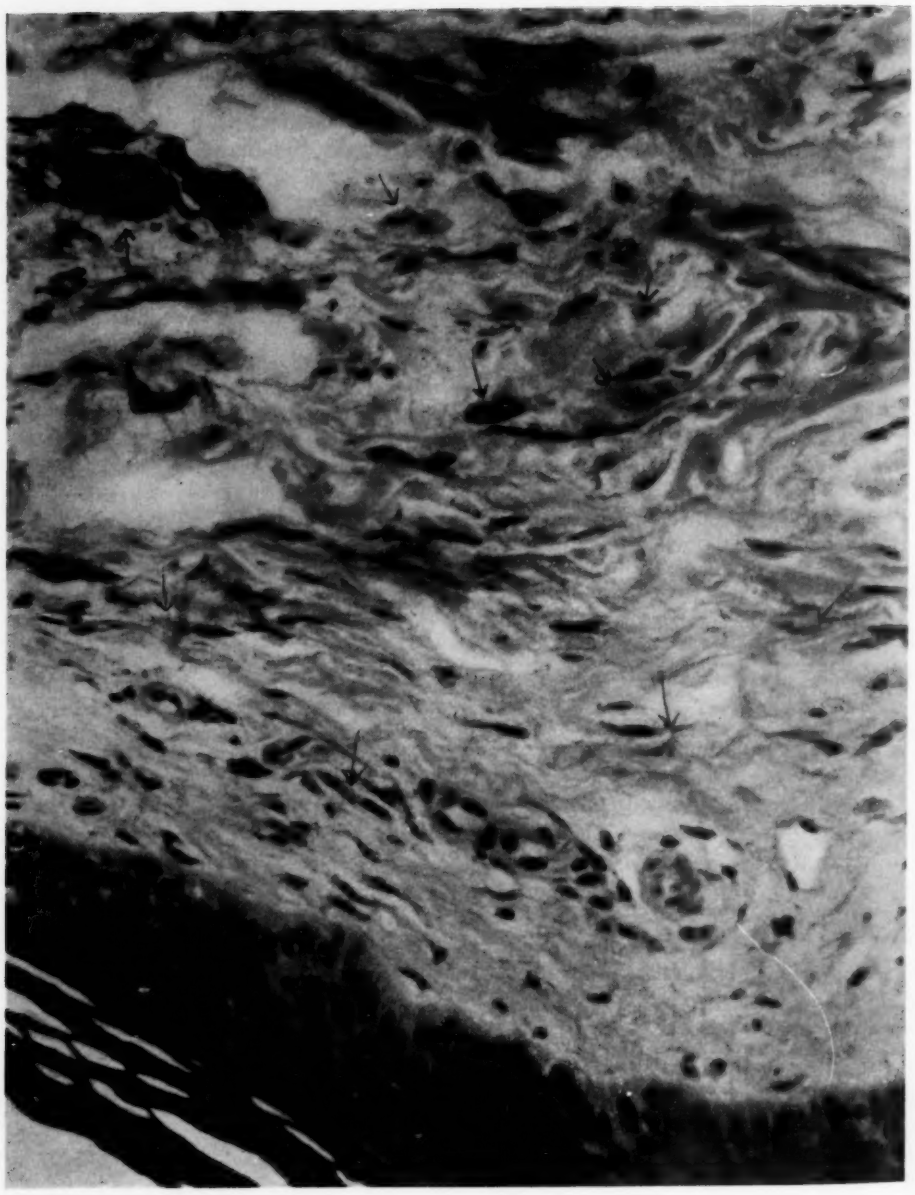


FIG. 1. *Case 1.* Hemochromatosis. Location of some of the pigmented histiocytes in the derma is indicated by arrows. Iron stain. × 700.

negative. Blood chemistry: urea nitrogen 12.04 mg.; sugar 115.6 mg.; and chlorides 511.5 mg. per 100 c.c. Glucose tolerance test: fasting blood sugar, 122.7 mg.; half-hour, 200 mg.; 1 hour, 243.8 mg.; 2 hours, 235.3 mg.; and 3 hours, 190.4 mg. per 100 c.c. The urine was negative for sugar in the first three specimens and positive in the last two. Five estimations of the basal metabolic rate between May 27 and July 4 varied from minus 30 to minus 5 per cent. Free HCl was absent in the fasting stomach, but was present after a test meal. Microscopic examination of a piece of skin removed from the right leg showed diffuse pigmentation of the derma by iron-containing pigment, compatible with a diagnosis of hemochromatosis.

Progress: Autogenous vaccine prepared from streptococci isolated from feces was administered, physiotherapy continued, and thyroid and pituitary therapy instituted. Progressive improvement was noted and the patient left the hospital July 26, 1932, feeling that he was in better health than he had been for years. He was advised to continue diet, autogenous vaccine, thyroid and pituitary therapy.

Diagnoses: (1) arthritis, chronic, infectious, moderate, with atrophic changes, first metacarpal-phalangeal joint, right, and first metatarsal-phalangeal joint, left, and slight atrophic changes, interphalangeal joints, both hands; (2) hemochromatosis, moderately severe; (3) pituitary gland, anterior lobe, hypofunction of, postadolescent, cause undetermined.

Comment: The diagnosis of hemochromatosis in this case is based on the following findings: (a) a hard, hypertrophic liver; (b) bronzing of the skin, with demonstration of hemosiderin on laboratory study; (c) definitely diminished glucose tolerance, as demonstrated by a diabetic blood sugar curve following glucose tolerance test, with glycosuria during the test; (d) slight enlargement of the spleen.

The diagnosis of pituitary insufficiency is believed warranted because of the apparently completely closed sella, atrophy of genitals with long-standing impotence, lowered basal metabolic rate, and dry, thickened skin. These latter findings might be properly interpreted as due to thyroid insufficiency, but the composite picture is rather one of pituitary disease (anterior lobe deficiency) with secondary thyroid hypofunction. The question arises as to what rôle, if any, the pituitary hypofunction played in the development of hemochromatosis in this case.

Case II

A white, married, male physician, 40 years old, was admitted to the Walter Reed Hospital December 12, 1932. His family history was negative.

Personal History: There was nothing of importance noted except liberal indulgence in strong alcoholic liquors for many years.

Present Illness: This patient had been in good health until about December 1, 1932, when he noticed that his feet seemed swollen. This swelling increased in amount, gradually ascending both legs, until about December 5 it reached his waist. Then he noted that his abdomen was getting larger. He stated he had had no other symptoms, but that about eight months before for some unaccountable reason, he had lost 40 pounds in weight (from his usual weight of 220 pounds). He was 70 inches tall, and had remained at about 180 pounds during the past eight months. On admission to the hospital he complained of swelling of feet, legs and abdominal wall, and of pressure in abdomen which became embarrassing to respiration. He remembered no symptoms suggestive of cardiac or renal disorder, nor any digestive disturbance until present swelling. At the time of examination he had abdominal discomfort and severe diarrhea.

Physical Examination: This patient was getting about in a wheelchair and was slightly dyspneic. There was marked edema below the knees and edema of back and abdominal wall. The skin had a brownish leaden hue most pronounced on the face, which exhibited also a slight dirty brownish mottling. The radial, brachial, and

FIG. 1. *Case I.* Hemochromatosis. Location of some of the pigmented histiocytes in the derma is indicated by arrows. Iron stain. × 700.

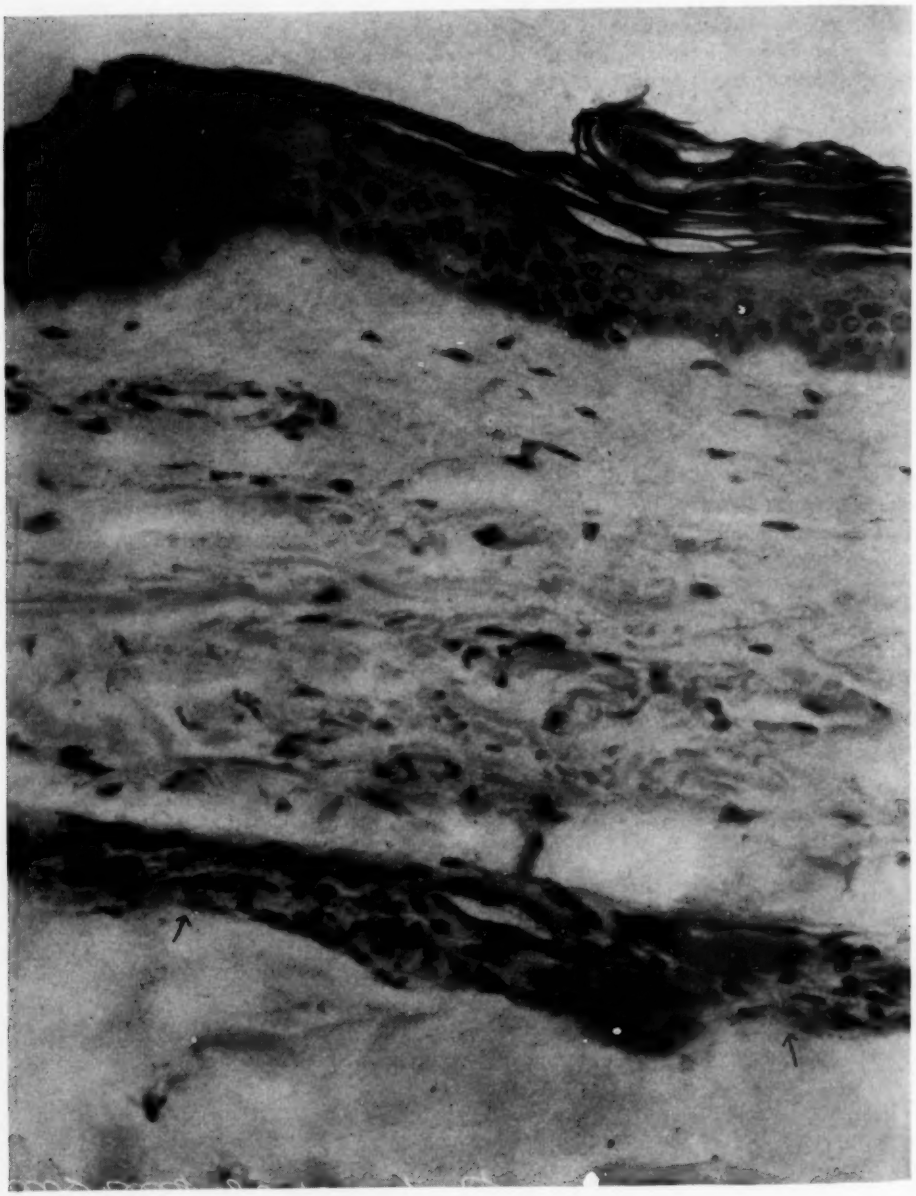


FIG. 2. *Case 2.* Hemochromatosis. Granules of iron pigment in histiocytes along the course of a small vessel in the derma. Iron stain. × 700.

retinal vessels were moderately sclerotic. The blood pressure was 130/68. Excursion of the lungs was limited by upward thrust of diaphragm due to ascites. The abdomen was distended, the greater prominence seeming to be above the waist, giving the impression of a tumor. Palpation for liver and spleen was unsatisfactory because of ascites. The right upper quadrant was slightly tender, but no masses were anywhere palpable. The superficial veins of the abdomen were enlarged. Bilateral mucosal ulcerations were seen on nasal septum. The sclerae were moderately icteric. *Roentgen-Ray* of the chest revealed abnormally high diaphragm, enlargement of hilus and increased root branch markings, but no infiltration or consolidation.

Laboratory Findings: Fifteen urinalyses were negative except for albumin in one of them and rarely a granular cast. Specific gravity range was between 1.009 and 1.026. Four specimens were examined for hemosiderin, and all were positive. Feces showed occult blood, but no ova or parasites. Red blood cell count, 3,330,000; white blood cells 13,000; Hgb. 75 per cent, polymorphonuclear neutrophiles 77 per cent. Blood Wassermann and Kahn tests negative on three examinations. Blood chemistry: urea nitrogen 16.66 mg., sugar 113.6 mg. per 100 c.c. Culture of ascitic fluid yielded no growth. Blood icterus index 25. Examination of one section of skin for hemosiderin was negative, but subsequent examination of another section of the same biopsy specimen was positive.

Progress: Following abdominal paracentesis, an enlarged, hard liver could be palpated, but the spleen could not be felt. Residual ascites interfered with examination. Soon after admission a severe psychosis developed, which proved to be delirium tremens, and which cleared under treatment in close confinement. Abdominal paracentesis and diuretics resulted in marked reduction of the ascites and edema. At the time of his discharge from the hospital, January 27, 1933, he was much improved, ambulatory, and entirely recovered from his alcoholic psychosis.

Diagnosis: (1) psychosis, acute, alcoholic, delirium tremens, moderately severe; (2) hemochromatosis, moderately severe; (3) arteriosclerosis, generalized, moderately severe.

Comment: The diagnosis of hemochromatosis in this case is believed warranted by the following findings: (a) hypertrophic cirrhosis of the liver, with ascites; (b) laboratory demonstration of hemosiderin in all urines examined for this pigment (four specimens); (c) increased pigmentation of the skin, with hemosiderin found in the one piece of excised skin. (The biopsy specimen was obtained from the leg, where pigmentation was not pronounced and lacked the grayish-brown color seen in his face.)

Diabetes was not present in this case, although a blood sugar tolerance test was not done. As with most reported cases of hemochromatosis, protracted excessive ingestion of alcohol was a noteworthy feature.

FIG. 2. *Case 2.* Hemochromatosis. Granules of iron pigment in histiocytes along the course of a small vessel in the derma. Iron stain. × 700.

CASE III

A white married male, 41 years old, a soldier for the past 20 years, was admitted to the Walter Reed Hospital November 14, 1932. His family history was negative, and he had no children.

Personal History: He had had the usual childhood diseases, malaria in 1914, dysentery in 1914 (type unknown), sciatica for several years prior to tonsillectomy in 1928. He acknowledged excessive indulgence in alcohol over a long period of years, but claimed to have given it up the year before because of digestive disturbances which it aggravated.

Present Illness: Since dysentery in 1914, he has been subject to frequent attacks of indigestion manifested by severe flatulency, vomiting, frequent sour eructations, and alternating constipation and diarrhea. He drank heavily prior to 1932, but found that drinking aggravated his digestive symptoms. These gastrointestinal dis-

FIG. 3. Case 3. Hemochromatosis. Section of liver showing iron pigment deposits.

turbances have been getting rapidly and progressively worse since January 1932, and he has lost about 25 pounds in weight. He was under observation in this hospital from September 9 to September 13, 1930, because of acute alcoholism, and again from April 27 to June 15, 1932 with a diagnosis of chronic catarrhal gastritis. He had three non-vital teeth with extensive periapical resorption which he was advised to have extracted at his station, but this has not been done. Some improvement was maintained until October 10, 1932, when diarrhea developed (7 to 8 stools a day) with moderate tenesmus, but no blood or mucus was noticed.

On November 14, 1932, he awoke during the night with sharp pain in upper abdomen, which radiated behind the lower sternum. He noticed a slight dry cough and found that deep inspiration increased pain, which he thought was due to gas on stomach. An enema brought slight relief, but the pain persisted and he was sent to this hospital that morning.

Physical Examination: This patient was ambulatory and without fever but appeared to be in acute pain. His height was 65½ inches and weight 104 pounds, about 31 pounds under his usual weight. The skin showed marked increase in brown pigmentation, to which was added a slight leaden hue. The tongue was red, with a few superficial ulcerated areas. The blood pressure was 98/62. The abdomen was flat, firm, tympanitic in upper portion, and slight epigastric tenderness, but no masses. The liver was not enlarged and spleen not palpable. Dental focal infection was noted in three teeth. The nasal septum was deviated to left, but the sinuses were clinically normal. The tonsils were out, but hyperplastic tissue was seen in left fossa. The eyes were negative except for small amount of white exudative material in both physiological cups, suggestive of old optic neuritis. *Electrocardiogram* showed sinus bradycardia with slight sinus arrhythmia and P-waves of very low amplitude in all leads, but no definite evidence of cardiac disease.

Roentgen-Rays: Gall-bladder failed to visualize, although in May 1932, during a previous admission, it was normal. Gastrointestinal series and barium enema show nothing abnormal. A chest film and flat film of abdomen negative.

Laboratory Findings: Urinalyses were negative. The one specimen examined for hemosiderin was negative. Section of excised skin examined for hemosiderin also reported negative. Examination of feces revealed neither parasites nor ova. Cultures of stools were negative for *Endamebae histolytica* and for the typhoid-dysentery group. No tubercle bacilli were found in the sputum. On admission, the red blood cells numbered 3,420,000 with 70 per cent hemoglobin, but this steadily decreased until on February 18, 1933, there were 1,220,000 red cells with 40 per cent hemoglobin. The differential count was not remarkable and the smear negative for malaria. On November 15, 1932, the blood Wassermann test was reported plus-minus, and Kahn test single plus, but on recheck November 19, 1932, both were negative. Blood chemistry: urea nitrogen 14.42 mg.; glucose 90.9 mg., per 100 c.c. blood. Van den Berg negative. Blood icterus index 4.2. Basal metabolic rate plus 8 per cent. The glucose tolerance test gave a peculiar reading which was interpreted as failure of sugar absorption from the alimentary canal: fasting sugar 100.5 mg.; at the half hour 90.9 mg.; at 1 hr. 88.8 mg.; at 2 hrs. 102.5 mg.; at 3 hrs. 100 mg. per 100 c.c. blood; urine negative throughout the test.

Progress: A few days after admission, the blood pressure rose to 134/72, but slowly declined until on March 7, 1933, when practically moribund two days before death, it was 60/30. Addison's disease, hidden neoplasm, atrophic cirrhosis of liver, and hemochromatosis were all suspected in this case. The patient received treatment with Eschatin (P. D. & Co. preparation of adrenal cortical extract) and with cortin manufactured by the Army Medical School, with distinct temporary improvement. Restriction of this adrenal cortical extract resulted in rapid and severe relapses. These therapeutic tests convinced observers that the patient's life was prolonged by the administration of this substance. Death occurred March 9, 1933.

FIG. 3. *Case 3.* Hemochromatosis. Section of liver showing iron pigment deposits.

Diagnosis: Although hemochromatosis was suspected in this case, a clinical diagnosis was not warranted, in view of failure to demonstrate hemosiderin in either the specimen of urine or skin section submitted for such examination. Therefore clinical diagnoses were rendered as follows: (1) Addison's disease; (2) bronchopneumonia, acute, terminal, both lower lobes; (3) enteritis, subacute, ulcerative, cause undetermined.

Autopsy Findings: The liver weighed 1150 gm.; its capsule was smooth, color dark red, and edges sharp. The cut surface was much darker than normal and markings were almost obliterated. The pancreas weighed 90 gm., colored a peculiar reddish-brown both through its capsule and on section. The spleen weighed 110 gm.; its capsule was slate color. The cut surface paler than usual and the pulp difficult to remove by scraping. The adrenals were small and on section, the cortices were pale yellow and narrow; the medullae were a dirty dark brown and diffluent.

Anatomical Diagnoses (based on gross and microscopic postmortem findings): (1) hemochromatosis; (2) bronchopneumonia, acute, terminal, hypostatic, lower lobes, both lungs; (3) cirrhosis, atrophic, pigment, of liver; (4) pigment (iron) deposition in liver; (5) pigment deposition (lipochrome, "wear and tear") in heart, adrenals, testes, intestine, and pituitary; (6) brown atrophy of heart; (7) enteritis, chronic, ulcerative, of ileum, cause undetermined; (8) emaciation and skeletal muscular atrophy; (9) aplastic bone marrow; (10) pleuritis, fibrinous, bilateral, slight; (11) decubitus, sacral; (12) atrophy of testicles.

Comment

There was much less clinical evidence of hemochromatosis in this case than in the first two cases, but postmortem examination proved conclusively the existence of this disease. A pathological diagnosis of Addison's disease was not made, and it is questionable whether the composite picture justifies such a diagnosis. Adrenal insufficiency unquestionably existed, but it is debatable whether or not the hemochromatosis was responsible for the clinical picture of Addison's disease (not limiting the latter term to a tuberculous infection of the adrenals). This case suggests that hemochromatosis may be a rare cause of Addison's disease, just as hemochromatosis may be a rare cause of diabetes. Abnormal deposition of iron pigment was not demonstrated in either the adrenals or pituitary in this case. However, the question arises whether the iron pigment might not have been present in those structures in masked form, not demonstrable by the usual staining reactions. Sheldon [33] found such excess of iron in the central nervous system of his case, not demonstrable by ordinary staining methods.

Summary

Three proved cases of hemochromatosis, recognized on the Medical Service of the Walter Reed General Hospital within a period of 12 months, arouse suspicion that the disease is not as rare as the literature indicates.

Two of these cases were recognized clinically, and were discharged to their own care after reaching maximum hospital benefit. The third case progressed to a fatal termination in hospital and, while the diagnosis was suggested, because of failure to demonstrate hemosiderin in either urine or skin it could not be proved until autopsy.

The generally accepted diagnostic triad includes: (*a*) grayish-brown pigmentation of the skin; (*b*) cirrhosis of the liver (sometimes atrophic, but usually hypertrophic); (*c*) diabetes mellitus. This triad need not be observed to establish a diagnosis. The diabetes may be lacking, dependent on the degree of pigment (iron) degeneration and fibrotic replacement of islet tissue in the pancreas.

The skin pigmentation, which is not always observed, is due partly to the deposition in the skin of an iron-containing derivative of hemoglobin, hemosiderin; and partly to an increase in the normal melanin of the skin. It is believed that the increased melanin may be incident to adrenal impairment brought about by fibrotic changes.

Pigmentary cirrhosis of the liver is the one constant feature of this disease. Splenic fibrosis with moderate enlargement is usually present, but not always demonstrable clinically.

Pituitary involvement was found in two of the cases here reported (Cases 1 and 3) but was not searched for in Case 2. The two patients in whom pituitary involvement was demonstrated also had bilaterally atrophic testicles.

The history of immoderate indulgence in alcohol in these three cases supports the views of other writers that alcoholism is in some way an important etiologic factor. No history indicative of copper poisoning was elicited from these patients.

Conclusions

1. Hemochromatosis is not a form of diabetes, as was thought by the older writers, but is one of the rarer causes of diabetes mellitus. Few cases of diabetes are caused by the much rarer hemochromatosis, but the latter disease usually does cause diabetes sooner or later.

2. Addison's disease may be simulated by the skin pigmentation, or adrenal insufficiency may be a real complication of hemochromatosis, dependent on pigmentary fibrosis of the adrenals.

3. Pituitary (anterior lobe) insufficiency may be an etiologic factor, but it is more likely a complication of hemochromatosis dependent on pigmentary fibrosis of the hypophysis, and is more prone to occur in patients with small sellas or otherwise exhibiting tendency to pituitary hypofunction.

4. To promote more widespread recognition of this disease, hemochromatosis should be considered in every case of diabetes mellitus, every case of cirrhosis of the liver, and every case of abnormal pigmentation of the skin. The diagnostic triad is encountered rarely, it is true, and even then its significance may be overlooked.

5. Some investigators have shown that copper poisoning is one cause of hemochromatosis. This should be borne in mind when prescribing copper therapeutically, as is so frequently done in combination with iron. It has been assumed that in copper therapy the mobilization of iron for hemoglobin building is facilitated. If also, as a result of copper therapy, elimina-

tion of iron is retarded and deposition of iron in the tissues is augmented, copper may not be so beneficial as hitherto believed. It is quite possible, however, that in the therapeutic dosage in which it is used in the treatment of anemia, copper exercises no such deleterious effect.

6. More careful research is indicated concerning the action of copper and iron, the effect of the former on hematopoiesis, and to determine whether, in therapeutic dosage over long periods of time, it may produce pigmentary cirrhosis.

7. Until more conclusive experimental and clinical facts are available, caution should be exercised in the dosage and continuity of administration of the various copper-and-iron compounds which now are enjoying such popularity.

REFERENCES

1. Alden, A. M.: A macroscopic test for hemochromatosis, Proc. Med. Assoc. Isthmian Canal Zone, 1916, Mt. Hope, 1917, ix, 138.
2. Althausen, T. L., and Kerr, W. J.: Hemochromatosis; report of three cases with results of insulin therapy in one case, Endocrinology, 1927, xi, 377–422.
3. Barber, H.: Case of hemochromatosis, Guy's Hosp. Rep., 1929, lxxix, 45–48.
4. Blanton, W. B., and Healy, W.: Hemochromatosis, Arch. Int. Med., 1921, xxvii, 406–420.
5. Callender, G. R.: Hemochromatosis, Internat. Clin., 1928, ii, 268–270.
6. Chandler, L. R.: An attempt to produce hemochromatosis experimentally, Proc. Soc. Exper. Biol. and Med., 1920–21, xviii, 24.
7. Cheney, G.: Hemochromatosis in a Japanese; case report, Calif. and West. Med., 1928, xxviii, 224.
8. Constam, G. R.: Case of hemochromatosis refractory to insulin, Proc. Staff Meet. Mayo Clin., 1928, iii, 225–227.
9. Critchlow, G. R.: Hemochromatosis associated with primary carcinoma of body of pancreas; report of case, Med. Jr. and Rec., 1929, cxxix, 67–68.
10. Donaldson, R.: Case of hemochromatosis complicated by primary carcinoma of liver, Guy's Hosp. Rep., 1929, lxxix, 28–44.
11. Dumphy, J. J.: Hemochromatosis, Boston Med. and Surg. Jr., 1924, cxc, 441–444.
12. Dunn, J. S., and Telling, W. H. M.: Discussion on hemochromatosis, Brit. Med. Jr., 1921, ii, 783–786.
13. Funk, E., and St. Clair, H.: Hemochromatosis, report of case with studies of copper content of liver, Trans. Assoc. Am. Phys., 1929, xliv, 134–142.
14. Hall, E. M., and Butt, E. M.: Experimental pigment cirrhosis due to copper poisoning; its relation to hemochromatosis, Arch. Path., 1928, vi, 1–25.
15. Hanot, V., and Chaufford, A.: Cirrhose hypertrophique pigmentaire dans le diabète sucré, Rev. de méd., 1882, ii, 385–403.
16. Hartman, C. C.: Hemochromatosis, Atlantic Med. Jr., 1926, xxix, 239–240.
17. Heald, S. L.: Hemochromatosis, Brit. Med. Jr., 1922, ii, 542.
18. Howard, P. C., and Stevens, F. A.: The iron metabolism of hemochromatosis, Arch. Int. Med., 1917, xx, 896–912.
19. Keith, W. D., and McNair, A. Y.: Hemochromatosis, diabetes mellitus, primary carcinoma of liver, Canad. Med. Assoc. Jr., 1930, xxii, 528–532.
20. Krall, P. M., and Ginsberg, A. M.: Hemochromatosis; report of case with postmortem findings, Jr. Kansas Med. Soc., 1929, xxx, 155–160.
21. Mackereth, J. G.: Case of hemochromatosis, N. Zealand Med. Jr., 1932, xxxi, 408–409.
22. Mallory, F. B., Parker, F., Jr., and Nye, R. N.: Experimental pigment cirrhosis due to copper and its relation to hemochromatosis, Jr. Med. Res., 1920–21, xlii, 461–490.

23. MANNING, D. F.: Hemochromatosis, Jr. Missouri Med. Assoc., 1925, xxii, 390–393.
24. MCCLURE, C. W.: Metabolism in a case of hemochromatosis, Arch. Int. Med., 1918, xxii, 610–616.
25. MILLER, R.: A case of hemochromatosis, Clin. Jr. Lond., 1911–12, xxxix, 101–103.
26. MILLS, E. S.: Hemochromatosis with special reference to its frequency and to its occurrence in women, Arch. Int. Med., 1924, xxxiv, 292–300.
27. MOELLER, F. W., and HUTTON, J. H.: Hemochromatosis in woman, Illinois Med. Jr., 1926, xlix, 146–148.
28. MUIR, R.: Hemochromatosis and bronzed diabetes, Trans. Royal Med.-Chir. Soc., 1922, xv, 107.
29. ORR, J. W.: Primary carcinoma of liver in case of hemochromatosis, Lancet, 1930, i, 1400.
30. ROUS, P., and OLIVER, J.: Experimental hemochromatosis, Jr. Exper. Med., 1918, xxviii, 629–644.
31. ROSE, W. J., and BOWEN, B. D.: Case of hemochromatosis, Bull. Buffalo Gen. Hosp., 1929, vii, 3–9.
32. RUSSELL, E.: Hemochromatosis, Med. Jr. Australia, 1925, i, 251–253.
33. SHELDON, J. H.: Iron content of tissues in hemochromatosis, with special reference to brain, Quart. Jr. Med., 1927, xxi, 123–137.
34. SMITH, E. B.: Hemochromatosis, Med. Times and Long Island Med. Jr., 1931, lix, 93.
35. SPRUNT, T. P.: Hemochromatosis; a report of three cases and a discussion of the pathogenesis, Arch. Int. Med., 1911, viii, 75–129.
36. TEDSTROM, M. K.: Hemochromatosis; report of case, Calif. and West. Med., 1930, xxxii, 102–104.
37. VON RECKLINGHAUSEN: Deutsch. Natfl. Tagebl., 1899, 324.
38. WILSON, S., and WEISER, F. A.: Hemochromatosis; report of a case with autopsy, Grace Hosp. Bull., 1925, ix, 1–13.
39. WINNETT, E. B.: Hemochromatosis treated with insulin, Jr. Iowa Med. Soc., 1928, xviii, 212–216.
40. DARNALL, J. R.: Hemochromatosis, a possible danger of copper therapy, Military Surgeon, 1933, lxxiii, 70–73.

PHILADELPHIA AND AMERICAN MEDICINE

THE approaching annual meetings of the American College of Physicians, to be held in Philadelphia, will bring the members of this College back to the cradle of organized medicine in this country. If a cradle were all that the city of Philadelphia had to offer the visiting physician, it is obvious that the meetings would, in all probability, have been scheduled elsewhere. The truth in our case is, of course, that today Philadelphia's physicians welcome their colleagues not to a city of the past, but to one into which the destiny which broods over cities has breathed a timeless and unquestioned devotion,—that towards the art of medicine.

Philadelphia, in size the third city of the country, vies with Chicago for first place in the number of recognized medical schools, each having five. The statistics on hospitals and physicians in the three cities are approximately in proportion to their population.

Your ever affect.e Brother
John Morgan

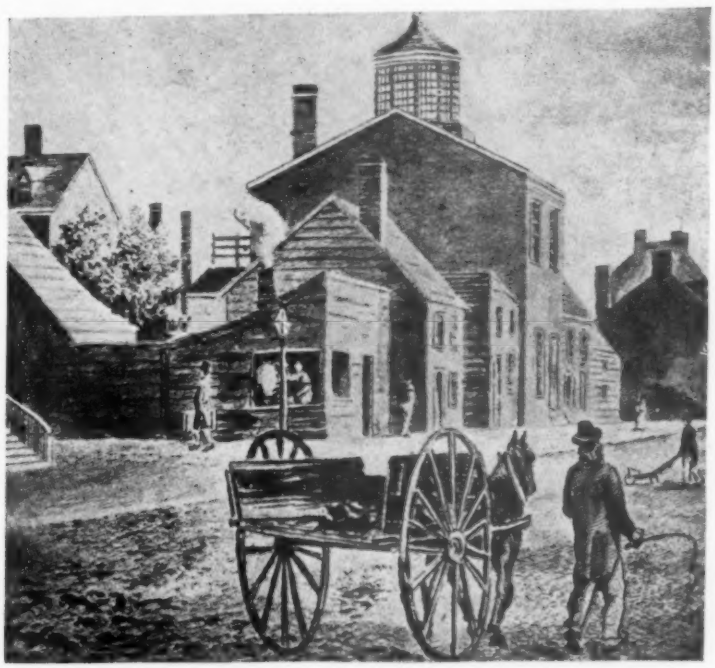
DR. JOHN MORGAN, 1735–1789. A.B. 1757, College of Philadelphia; M.D. 1763, Edinburgh.

The Medical School of the University of Pennsylvania * in September of this year, holocaust and taxes not intervening, will undertake for the one hundred and seventieth year to offer organized medical instruction to the youth of this and other lands. The record is unique in this country. This first medical school in the colonies came into being in 1765 as the Department

* The following material has been assembled and in large part taken verbatim from the Reports and Announcements and from individual histories of the various institutions.

of Medicine of the College of Philadelphia, largely through the efforts of a distinguished Philadelphia physician, John Morgan, who, appropriately, was elected to the first medical professorship in the colonies. Morgan belonged to that first great group of Philadelphia physicians whose superb vigor of mind and body, and whose devotion to the progress of American medicine, left their impress indelibly upon the face and in the soul of the city.

On June 21, 1768, ten students walked out of the commencement exercises of the College of Philadelphia (now the University of Pennsylvania), with the first medical degrees granted by the first medical school in the country. Since that day, 16,366 other youths have followed in their footsteps.



MEDICAL SCHOOL OF THE UNIVERSITY OF PENNSYLVANIA (SURGEONS' HALL), 1765–1802. (East side of Fifth Street, between Liberty and Walnut Streets.)

The buildings that have housed the Medical School have been several; the catalogue of professors is long and illustrious. Over the earlier homes it would not be profitable at this time to pause. From the list of professors, piety and affection demand that we single out at least the names of William Shippen, Jr., Benjamin Rush, James Woodhouse, Benjamin Smith Barton, Caspar Wistar, Nathaniel Chapman, Philip Syng Physick, William P. Dewees, William Edmonds Horner, Robert Hare, George B. Wood, Hugh Lenox Hodge, Joseph Leidy, D. Hayes Agnew, William Goodell, William Pepper, Alfred Stillé, William Osler, Richard A. F. Penrose, H. C. Wood, Leonard Pearson, C. L. Leonard, John Ashhurst, George W. Norris, Louis Duhring, J. William White, George A. Piersol, and E. T. Reichert.

In 1873 the University moved to its present location in West Philadelphia adjoining the grounds of the Philadelphia General Hospital. The University Hospital was erected on the campus at that time. The Laboratory of Hygiene was built in 1892, and the Laboratories of Pathology, Physiology, and Pharmacology were formally opened in 1904. In 1928, however, there was attached to their building a splendid five-story structure which now houses the Departments of Anatomy, Physiological Chemistry, Research Surgery, and the Anatomy Department of the Graduate School of Medicine.

MARTIN MALONEY PAVILION, headquarters of the Research Foundations of the University of Pennsylvania School of Medicine. (Thirty-Sixth and Spruce Streets.)

In the same year, work was begun on the Maloney Pavilion. This nine-story building at Thirty-Sixth and Spruce Streets connects with the Hospital and furnishes quarters for the William Pepper Laboratory of Clinical Medicine (originally this laboratory occupied a building erected for it in

1894, the first unit of its kind in the country), the Department of Research Medicine, the Eldridge Johnson Department of Biophysics, various special diagnostic clinics of the Medical Out-Patient Department, special wards for cases under observation by the Department of Research Medicine, and about 25 private rooms.

The Wistar Institute of Anatomy and Biology, at Thirty-Sixth Street and Woodland Avenue, incorporated in 1892, was the first American University Institute devoted to advanced study and research in anatomy and biology. The Henry Phipps Institute for the study, treatment, and prevention of tuberculosis, at Seventh and Lombard Streets, was established in 1903, the first fully organized and equipped institution of the kind with University connection.

Other notable "firsts" of which the School of Medicine is entitled to boast include the graduate courses in public health leading to the degree of Doctor of Public Health; a separate building for research in, and the teaching of, hygiene; the Department of Research Medicine in which the workers are expected to devote practically their entire time to research.

Laboratory of Anatomy and Physiological Chemistry (University of Pennsylvania School of Medicine).

The School includes in addition to the Research Foundations mentioned above, the Robinette Foundation, the Gynecean Hospital Institute of Gynecologic Research, and the Laboratory of Dermatological Research.

The University Hospital, which is an integral part of the School, and whose staff is drawn entirely from the clinical members of the medical faculty, was the first in the country to be built by a university for the use

of its medical school. There are at present available in it 457 ward beds as well as 98 private and 38 semi-private beds. During the fiscal year of 1933 to 1934, there were 9,368 bed patients, 103,410 visits to the out-patient departments, and 7,879 surgical operations were performed. Students of all four classes are taught here every clinical subject.

This medical school, in brief, in the course of nearly 170 years of active life has met with amazing resource and courage the demands of our increasingly complex civilization, so that today its equipment enables it to offer its students every advantage of theoretical, practical, and research study. Age has indeed not withered, nor custom been allowed to stale.

GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA.

The University's Graduate School of Medicine, located at Nineteenth and Lombard Streets, was organized in 1916 by a merger between the University and the old Medico-Chirurgical College of Philadelphia, which had been founded in 1881. In 1918 the Philadelphia Polyclinic and College for Graduates in Medicine merged with the Graduate School of Medicine and formed the Polyclinic Section. Later additions of assets included the Diagnostic and Howard Hospitals, and the North American Sanitorium.

The Graduate School of Medicine today is, administratively, a separate university unit, or association of units, operating in complete coöperation with the School of Medicine, and, like the latter, is administered ultimately by the University's vice-president in charge of medical affairs. Its students are suitably qualified physicians who become, substantially, academic, clinical, or research assistants or understudies of the members of the faculty in medical activities throughout the city, intramurally and extramurally. For an essential feature of the Graduate School's "Pennsylvania Plan" of graduate medical education is the upbuilding of an extensive coöperation between the central organization, that is, the Graduate School, and extramural medical organizations and their staffs. At present, 50 of Philadelphia's medical organizations are found to be thus coöperating. The Graduate Hospital, covering more than one city block, is the clinical teaching center of the school. Its approximate normal monthly activity rate is 10,000 bed days, 600 operative cases, and 12,000 out-patient visits. The Graduate School of Medicine of the University of Pennsylvania is today the only institution of its kind in Philadelphia.

Jefferson College and Hospital. Philadelphia's second medical college, in point of time, is an equally vigorous ancient of the second generation. This is the Jefferson Medical College, founded in 1825, as the Medical Department of the Jefferson College of Canonsburg, Pa. Its first class was graduated in the following year. In the intervening 108 years, it has conferred a medical degree upon approximately 16,000 of its students, a number not far short of that produced by its older sister.

The College today occupies a handsome building on Walnut Street, just west of the old College building at Tenth and Walnut Streets, where now is situated its Curtis Clinic. The College building, opened in 1929, represents, like the Maloney Pavilion of the University of Pennsylvania, a thoroughly modern response to the technical developments of the day as they affect the equipment for medical instruction and research. Herein are contained, in addition to administrative offices, professors' rooms, work rooms, recitation, lecture, demonstration, and assembly rooms, laboratories large and small, for the use of the various departments, a library, and the College Museum.

The Jeffersonians may claim that systematic clinical methods of instruction were first inaugurated, as far as the United States is concerned, within the walls of their college, since a dispensary was therein established in advance of the opening session; and it was from cases which it supplied, that Dr. George McClellan, a leading surgeon and teacher of his day, and the founder of the College, conducted the first surgical clinics in the country.

The clinical teaching is today carried on largely in the College's Hospital, adjacent to the College itself. This building, opened in 1907, with a capacity of about 377 ward beds, in addition to the private rooms, offers every facility for this purpose. Under the supervision of professors and experienced instructors, students are required to participate in operations and to assist in the administration of anesthetics. When the interests of the pa-

tient are not thereby jeopardized, the student may follow the case from admission to discharge.

CURTIS CLINIC OF THE JEFFERSON COLLEGE AND HOSPITAL, WALNUT AND TENTH STREETS, WITH THE COLLEGE BUILDING AT THE LEFT.

The Curtis Clinic, adjoining the College, and conforming to it architecturally, is the out-patient unit. The building is planned so as to group the various medical, surgical, and specialty divisions. The Hospital's central location insures an exceptionally large service demand, particularly in the out-patient department. The surgical division of this department received in the year ending May 31, 1933, 115,757 visits and the medical division, 90,706, giving a total out-patient service of 206,463 visits.

In 1924 the Samuel Gustine Thompson Annex to the Jefferson Hospital was opened. This building contains the teaching clinical amphitheater, seating 550, a maternity department, bronchoscopic wards, and a teaching clinical laboratory upon the roof. The Department of Anatomy, including Descriptive and Practical Anatomy, Histology and Embryology, and

Anatomy as applied to Medicine and Surgery, is housed in a building of its own at Clinton and Eleventh Streets, a few blocks from the College. This is the Daniel Baugh Institute of Anatomy, containing laboratories, a museum, amphitheaters, and a notable departmental anatomical reference library. The Department for Diseases of the Chest is likewise set apart, in a building at 238 Pine Street. Although the activities here are concerned largely with the problem of tuberculosis, other related conditions are studied and treated. Twelve students are selected from the fourth year class to reside in the department and assist in the preparation of histories and in the special study of patients.

Jefferson's faculties, which weathered severe storms in the early days, have contained some of the most distinguished Philadelphia physicians of national reputation: such men, for instance, as George McClellan, already mentioned, John Eberle, Daniel Drake, Nathan R. Smith, Robley Dunglison, Joseph Pancoast, J. K. Mitchell, Thomas D. Mütter, Charles D. Meigs, Franklin Bache, Samuel D. Gross, Samuel H. Dickson, Robert E. Rogers, the younger Gross, J. M. DaCosta, Roberts Bartholow, W. W. Keen, Hobart Amory Hare, and J. C. DaCosta. The College's history is a colorful one, and its achievements loom large in the history of the city's and the nation's medical life.

Hahnemann Medical College and Hospital. In 1845, homeopathy had practitioners (about 250 in number) in 22 states, but no institution where homeopathy was taught. Its doctrine, in fact, was promulgated under a cloud of disapproval by the medical profession, which culminated in resolutions passed, in 1847, by the newly formed American Medical Association, tending to stigmatize it as irregular. It was in an attempt to gain legal recognition for the system that the Homeopathic Medical College of Pennsylvania, the oldest of its kind in the world, was founded in 1848. In 1869 this college was consolidated with the Hahnemann Medical College of Philadelphia under the corporate name of the Hahnemann Medical College of Philadelphia, and in 1885 the corporation of the Hahnemann Medical College and Hospital of Philadelphia was brought by merger into existence and located at its present site.

With admirable sincerity of purpose the College has pursued its course, constantly strengthening its base and widening its curriculum in line with the developments in the fields of medicine. Its requirements today include two years of college work as a minimum, preference being given those applicants with more preparation. The Medical School offers a standard four years' course, and confers upon its graduates, by provision of its state charter, two degrees, those of Doctor of Medicine and Doctor of Homeopathic Medicine. Special attention is given, of course, to the Department of Materia Medica and Therapeutics and to the principles of Hahnemann, Hering, Dunham, and other noted men in the field, but the prime object of the school is to give a broad and thorough medical education.

The College building contains lecture rooms, a large library and museum,

laboratories, rooms for operative surgery and practical obstetrics, the administrative and faculty offices and reading rooms. The College Library may be divided into two departments. One contains about 15,000 volumes and is especially of historical interest. Here are found Dr. Hering's notable

HAHNEMANN MEDICAL COLLEGE AND HOSPITAL. (Broad above Race Street.)

collection of the writings of Paracelsus, Dr. A. R. Thomas' collection of very old and rare anatomical books, all of Hahnemann's works in the original and the most complete library of homeopathic literature in existence. The other constitutes a valuable working library and reading room for students and contains a file of the principal medical and scientific journals. Investigation in medical literature is considered an essential part of the college course.

The new Hahnemann Hospital, 20 floors in height, was opened in 1928 and has a total capacity of 700 beds, 370 of which are public. Over 12,000 bed patients are treated in a year, and during the past year 120,000 visits were made to the out-patient department. The Hospital is equipped with electrocardiographic, fluoroscopic, basal metabolism and clinical laboratories. The arrangements are such that the operating units are coördinated on the same floor with the roentgenological department, the clinical and pathological laboratories of the Hospital being on the floor directly below. As with

the other schools and hospitals which we have mentioned, the faculty of the School and the staff of the Hospital are one, and the clinical material presented by the Hospital is directly available for teaching purposes and is used constantly.

The tendency of the day in this country is unquestionably toward greater uniformity in medical instruction, and to the advance along this line Hahnemann College has devoted itself with obvious success.

Woman's Medical College of Pennsylvania. The position of women in American medicine would probably be as uncomfortably anomalous today as it was in the early years of our national life, had there not come quietly into existence in 1850, in Philadelphia, an institution quaintly called, in the terminology of the day, the Female Medical College of Pennsylvania. This was the first college in the world regularly organized for the medical education of women, and it is still the only medical school in the United States exclusively for women.

WOMAN'S MEDICAL COLLEGE. (Henry Avenue and Abbotsford Road.)

The opening session of the College found 40 students enrolled for instruction by a faculty of six, all men. The first class graduated numbered eight, of whom one, Dr. Ann Preston, was soon elected to the Chair of Physiology and Hygiene, the first woman to have a place on the faculty. Today over two-thirds, about 70, of the faculty are women.

It is to be expected that the problem of adequate clinical instruction would be a difficult one for the pioneers to overcome, and such indeed it was. In 1860 we find the first official reference to the founding of the Woman's Hospital of Philadelphia. A lack of foresight in the acquisition of its charter, however, led to a situation in which the College and the Hospital came under the management of dual groups, which hindered the use of the Hospital for clinical teaching. Fortunately, other clinical opportunities were opening up. On January 2, 1869, the distinguished Alfred Stillé prefaced his lectures in the amphitheater of the Philadelphia Hospital with these words:

"Ladies and Gentlemen: I have pleasure in meeting you today. It is the first time in my medical experience that I have had the opportunity of addressing women among the audience of my pupils. We are sometimes shocked at what is novel, simply because it gives us an unaccustomed impression, but in the present instance I must say that, so far as I am personally concerned, I not only have no objection to seeing ladies among a medical audience, but, on the other hand, I welcome them."

In 1869, likewise, the Board of Managers of the Pennsylvania Hospital came nobly to the rescue with an invitation to the women students to attend the clinical lectures at that institution. On November 6 of that year about 30 women students accepted the invitation, but presumably somewhat to their chagrin. The novelty was not only a shock to the male students of the Pennsylvania Hospital, but it was received with conduct on their part which quickly made of the incident a *cause célèbre*. The way of the pioneer, which is, in a sense, that of the transgressor, was ever hard.

The site and buildings of the present College and Hospital, opened in 1930 and occupying approximately 10 acres, present the former Female College of Pennsylvania, under its present title, as one of Philadelphia's distinguished medical institutions. The Hospital, containing 152 beds and 21 bassinets, is conducted by the Corporation under the professional direction of the faculty. A fully equipped heart clinic was opened in 1932 and a bronchoscopic clinic in 1933 to 1934. An out-patient clinic is conducted at Barton Dispensary, 1309 North Twenty-Second Street, as well as at the Hospital. The students enjoy many of the extramural privileges, such as the use of the Libraries of the College of Physicians and the Academy of Natural Sciences, and of various clinics, accorded their male colleagues. If the millennium has not yet been attained, that is a circumstance of which we are all, men as well as women, in one way or another the victims. Certainly, the work of the Woman's Medical College of Pennsylvania has contributed not a little toward defining the road forward.

Temple University School of Medicine. The Medical Department of Temple University was opened in 1901. It is, therefore, the youngest of Philadelphia's five recognized medical schools. No one, however, with even a bowing acquaintance with the country's medical schools will be deceived by that fact. Its status today as one of our major schools of medicine is uncontested. This position it has achieved in comparatively few years, through its success in drawing to it a distinguished faculty and in furnishing them and their students with the most modern equipment for research and instruction. Its success in attracting medical students may be gauged by the fact that, though the first-year class is limited to 100, in 1933 nearly 2000 applicants were considered by the Committee on Admissions.

If the annals of this school are as yet too brief to provide a historian's field-day, it should at least be pointed out that the Temple University School of Medicine was the first coeducational medical school to be established in

Pennsylvania. Its third graduating class, in fact, included two women. Thus far at least had we traveled since the embattled days of '69.

The present building occupied by the School was opened in 1930. It is situated on Broad and Ontario Streets, directly opposite the University's Hospital. Dispensaries and administrative offices share with the library the first and second floors. The various departments are housed in the third to sixth floors, while the seventh contains medical and research rooms and storage facilities for mammals, rodents, etc.

TEMPLE UNIVERSITY SCHOOL OF MEDICINE. (Broad and Ontario Streets.)

The Temple University Hospital, where most of the clinical teaching is done, is directly under the control of the faculty. It ranks with the larger institutions of its kind in the city in facilities and equipment, having a bed capacity of 469, which affords abundant material for every branch of clinical instruction. A laboratory building on the hospital grounds provides a well equipped clinical laboratory, an autopsy room, private laboratories for original research, and rooms for teaching purposes.

Temple University itself, founded in 1884 by Russell H. Conwell, celebrated the past year its fiftieth anniversary. The seal of the University bears the motto *Perseverantia vincit*. As one looks at the achievements of its medical school in so short a period, one is almost tempted to believe that perseverance, soon or late, if the object be a fair one, does win.

Philadelphia College of Pharmacy and Science. It would certainly not be fitting to close this brief survey of Philadelphia medical schools without

recalling to the visitor's attention the fact that the Philadelphia College of Pharmacy and Science, at Forty-Third and Kingsessing Avenue, today one of the leading institutions of its kind in the country, was also the first college of pharmacy in the new world. The history of this college, founded in 1821, in Carpenter's Hall, seat of the Provincial Assembly and of the first general Congress of the Colonies, covers practically the history of pharmaceutical education in this country. Its founding, by 68 druggists and apothecaries bent upon education by the masters of their craft, indicates once more the early and deep devotion of Philadelphia's medical groups to the highest development of their science. And it is by way of illustrating the high quality of instruction which has always been maintained in the College that we recall as members of its faculties George B. Wood, Joseph Carson, Franklin Bache (great-grandson of Benjamin Franklin), Robert Bridges, William Proctor, John M. M. Maisch, Samuel P. Sadtler, and Joseph P. Remington.

Hospitals. The hospitals which are directly connected with the various schools of medicine have already been briefly mentioned. We may be forgiven under the circumstances if from the many others we select for a brief introduction those which will be the most intimately involved in the forthcoming meetings.

The Pennsylvania Hospital. To those who have the fortune to see medicine in its historical perspective, the Pennsylvania Hospital is perhaps more than any other medical institution in the country a rich source of pleasure. One of the largest and most important hospitals in the city today, it yet retains both in its exterior and in its interior much that is evocative of its long and notable past. It is, in fact, the oldest hospital in the United States which was intended wholly for the sick and wounded and which has continued on its ancient site and maintained its original name. The accompanying lithographic illustrations by Philadelphia's celebrated son, the late Joseph Pennell, speak more directly of the continuing beauty and charm of the place than any words which we might use. The famous double staircase is pictured here, but not the old clinical amphitheater, first of its kind in America, the library, the notable paintings (including Benjamin West's "Christ Healing the Sick"), or many other carefully preserved witnesses of a distinguished life.

The founding of this Hospital was predominantly the work of Benjamin Franklin and his close friend, the physician Thomas Bond. The latter is remembered today also as the originator of the Bond splint for the treatment of fractures of the forearm, and for the invention also of an instrument for extracting foreign bodies from the esophagus, thus inaugurating what seems to have become an old Philadelphia custom.

The roster of the Hospital has always contained the names of many of the city's leading physicians—the Bonds, Morgan, Shippen, Jones, Rush, Physick, James, Parish, Otto, Ward, Pepper, Gerhard, Agnew, Packard, Ashhurst, Harte. This gratuitous service was instituted by the Hospital's

first physicians. It is estimated that the services performed by the Staff today are worth over $400,000 a year.

The divisions of the Pennsylvania Hospital today are the Department for the Sick and Injured, the Department for Mental and Nervous Diseases, and the Institute of the Pennsylvania Hospital. The Philadelphia Dispensary, founded in 1786, is now also carried on as part of the "Out-Patient Department of the Pennsylvania Hospital and Philadelphia Dispensary."

PENNSYLVANIA HOSPITAL FROM THE GROUNDS.

The Pennell drawings of the Pennsylvania Hospital, which appeared originally in "Our Philadelphia" are reproduced through the courtesy of Mrs. Joseph Pennell and the J. B. Lippincott Company, of Philadelphia.

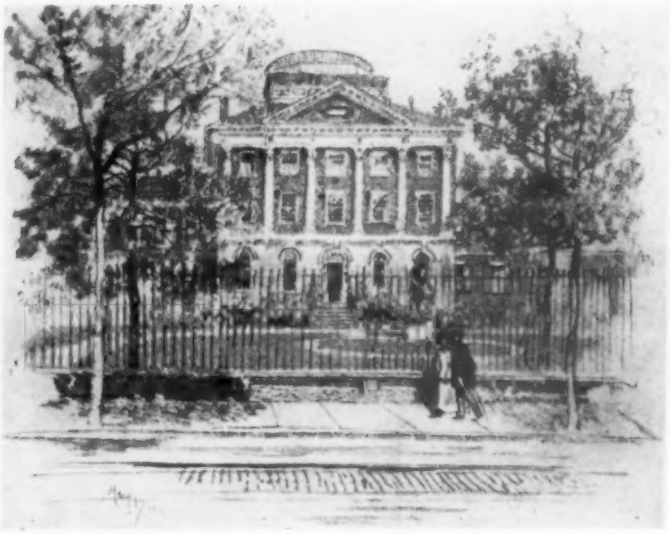
The Department for the Sick and Injured, at Eighth between Spruce and Pine Streets, occupies the site it first moved to in 1756. An interesting analysis of its service, as given in the Hospital's most recent Annual Report, indicates that during the year there was an application for either emergency or ward care every 14 minutes; a ward bed or a private room received a new patient every 84 minutes; the Out-Patient Department cared for a patient

every three and two-fifths minutes; the police patrols brought a patient to the door every five hours and 22 minutes; a surgeon performed an operation every two hours and four minutes. No further words are needed to show that this Department of the Hospital, which, like the Jefferson College Hospital, is in the center of the city, fulfills the extraordinary demands made upon it as courageously as it did in the days when it was a new institution in a New World.

THE DOUBLE STAIRWAY OF THE PENNSYLVANIA HOSPITAL.

The Department for Mental and Nervous Diseases and the Institute are reminders that the Pennsylvania Hospital from its origin was the pioneer in the Colonies in the treatment of the mentally unstable not as criminals but as patients suffering with mental disease, subject to individual treatment and eventual return to reason. This department was moved to its site in West Philadelphia, at Forty-Fourth and Market Streets, in 1841, and its first Superintendent, Dr. T. S. Kirkbride, so impressed his personality upon the

institution that, for many years, it was familiarly known as " Kirkbride's." The treatment of its more than 200 patients is naturally on an individual basis, planned after a comprehensive study of the patient, and employs such methods, depending on the diagnosis, as fever, occupational and physiotherapy, the Aschner treatment, music, recreation, etc. It may be of interest that the latest published statistics show that 36 per cent of those committed in the last year were diagnosed as having manic-depressive psychoses, while cases which set into no definite mould of mental disease constituted another 21 per cent.



PENNSYLVANIA HOSPITAL FROM PINE STREET.

The Institute, at Forty-Ninth and Market Streets, represents the Hospital's latest development in the line of treating mental conditions. The keynote of its work is that of prevention of mental and nervous illness. Here in quiet and comfortable surroundings the attempt is made to solve the emotional problems as much as possible by natural means under medical direction. Civic recognition of the work of the Institute was signalized in 1933 by the presentation of the Philadelphia Award to the Chief of Clinical Service and Medical Director of the Institute. The career of the Pennsylvania Hospital has been memorable in many ways, in none other perhaps so memorable as in its steady devotion to the understanding and healing of the mentally sick and injured.

Philadelphia General Hospital. The Philadelphia Almshouse was erected in 1731 or 1732. In 1835 it officially adopted the title " Philadelphia Hospital," which again gave way, in 1902, to the title it bears today, namely, " Philadelphia General Hospital."

The history of this institution from its earliest days as an alms- or

"bettering" house, receiving, in the older fashion, the poor, the sick, and the lunatic, to its position today as the largest hospital in the city and one of the largest in the country, forms one of the more remarkable chapters in the history of medicine in Philadelphia.

THE INSTITUTE OF THE PENNSYLVANIA HOSPITAL. (Forty-Ninth and Market Streets.)

Though the title "Philadelphia Hospital" was not adopted until 1835, there is ample evidence that a hospital department existed at the Almshouse from its early days. And the title adopted in 1835 was again curiously inconclusive in that the Almshouse and the Hospital continued to be located together at the present site of the Philadelphia General Hospital until 1920, when the Almshouse was removed to separate quarters away from the hospital grounds.

The earliest records of the Hospital, unfortunately not so well preserved as those of the Pennsylvania Hospital, show that the pre-Revolutionary attending physicians numbered many of the famous group so intimately connected with the founding and the early days of the Pennsylvania Hospital and the Medical School of the present University of Pennsylvania. Since those days the staff of the Hospital has included at one time or another Philip Syng Physick, Caspar Wistar, Benjamin Smith Barton, Nathaniel Chapman, T. C. James, Hugh Lenox Hodge, S. D. Gross, D. Hayes Agnew, William Osler (whose notable postmortem work was done here), S. Weir Mitchell, J. H. Musser, H. C. Wood, Louis A. Duhring, W. W. Gerhard (it was in this Hospital that he made his clinical observations on the differentiation of typhus from typhoid fever), DeForest Willard, and others of equal prominence.

When the Hospital moved, in 1834, to its present site and assumed officially the name " Philadelphia Hospital," it assumed unofficially the name " Blockley ", from the township in which it was placed, and this was the name by which it was commonly known, to which it still occasionally answers today. In 1834 it was supposed to accommodate 400 sick, 200 more, if necessary, and was difficult of access from the medical schools. Today it has a capacity of about 2700 beds and has as its near neighbor the Medical School of the University of Pennsylvania.

AN AERIAL VIEW, SHOWING THE UNIVERSITY OF PENNSYLVANIA TODAY (LEFT), THE PHILADELPHIA GENERAL HOSPITAL (RIGHT CENTER), THE STADIUM, AND THE CIVIC AUDITORIUM.

The greatest strides in the New Philadelphia General Hospital have been taken in the last 15 years. This period has seen the development of the out-patient clinics to which in the past year 44,642 visits were paid. Particularly noteworthy is the work being done in cardiology, in metabolism, in occupational diseases, in tuberculosis, in radiology, and in the neuropsychiatric, prenatal, and postnatal clinics. The Saturday morning clinics, for the general practitioners of the city, are a prominent feature of the Hospital's life today. Cases of special interest in the Hospital are drawn upon for material and some prominent physician, not necessarily of the staff, is invited to talk upon them.

This period has seen, also, the erection of a building for the adequate housing of the interns and resident physicians, and one for the care of the female tuberculous. The impressive proportions of the Philadelphia General Hospital today, an idea of which can be readily gained from the accompanying aerial view, and the notable work which it continues to do, are further tributes to the vigor and integrity of Philadelphia's medical men who have had occasionally, in making this Hospital possible, severe political battles to wage in order to maintain adequate scientific independence and progress.

CHILDREN'S HOSPITAL. (Bainbridge Street entrance.)

The Children's Hospital. The Children's Hospital of Philadelphia, at Eighteenth and Bainbridge Streets, in the past year opened another wing (Rush) of its projected final group. This well emphasizes the continuing growth of the country's oldest hospital designed exclusively for children, established in 1855, and the third such hospital in the world. The first home of the Hospital had accommodation for 12 patients; the present Hospital, opened in 1916, has a capacity of 156 beds.

The primary purpose of the Hospital was to care for children suffering from diseases which could not be properly treated in their homes. An interesting commentary on the changes of direction which the progress of medicine takes is the Hospital's Department for Prevention of Disease, inaugurated in 1914 as an outgrowth of a previous Social Service Depart-

ment. This Department, the first of its kind in any hospital in America and one which draws visitors from all over the world, treats annually both in their homes and in the clinics well over 100,000 patients. This, in addition to an annual regular out-patient service of over 40,000 visits and an in-patient roll of approximately 3000 patients, is sufficient evidence of the remarkable service which this Hospital gives to the children of Philadelphia. As a further development in the general field of Child Welfare, the Hospital established in 1923 a Child Guidance clinic. This clinic was designed to examine and recommend the right management of problem children,

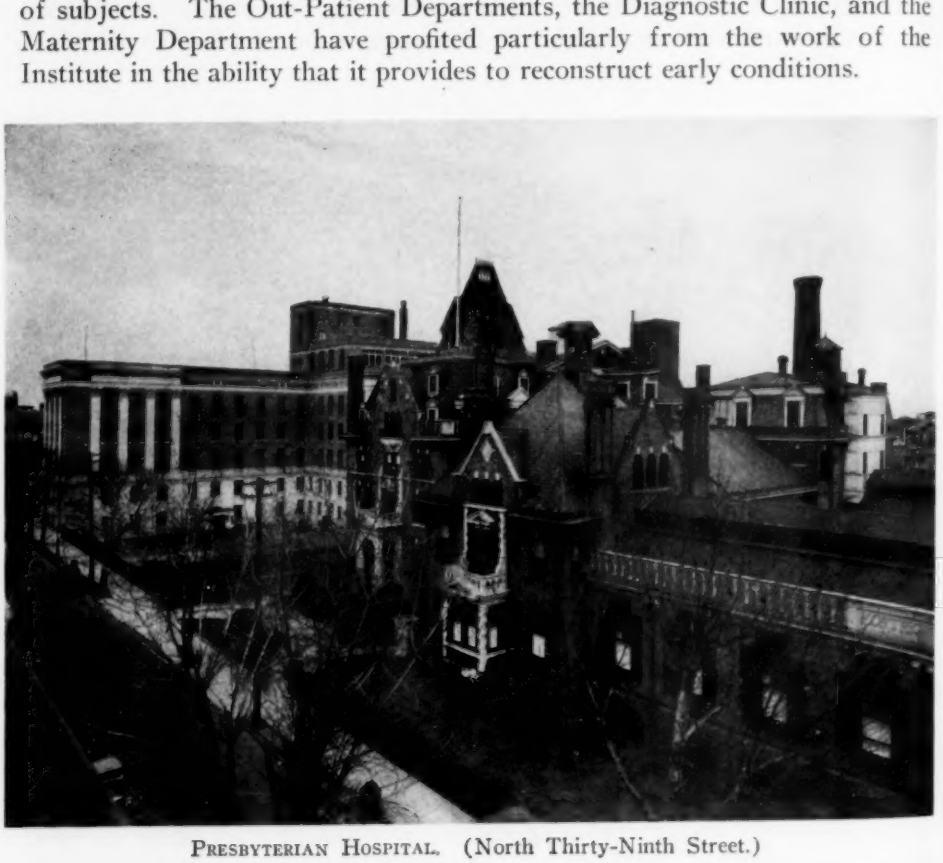
LANKENAU HOSPITAL. (Girard and Corinthian Avenues.)

truants, potential criminals, and other misfits. It has under its guidance constantly over 800 of these children. Philadelphia, once again, has proved itself a pioneer in the now accepted doctrine, proposed so early in our medical history by the Pennsylvania Hospital, that the physician can not exclude from his realm the unsound mind, no matter how sound the body.

Lankenau Hospital. The Lankenau Hospital, incorporated in 1860, opened for patients in 1866 as the German Hospital of the City of Philadelphia. Its present name honors its second President, John D. Lankenau, whose personal care and generosity are credited with being the chief agents through which it reached its present standing among the city's hospitals.

Originally designed as a hospital in which the German people of Philadelphia might be treated by physicians and nurses who could speak their native tongue, the Hospital has inevitably come to serve a wider function. Though the Hospital is excellently equipped for its annual in-patient service demand of about 4000 patients and an out-patient visit total of about 37,000, probably its chief interesting feature is its Research Institute. This was built in 1925 by the late Rodman Wanamaker, at the cost of about half a

million dollars. The activities of the Clinical Laboratories of this Research Institute include in a year about 60,000 examinations of all types. A Division of Art and Photography records the completion of numerous drawings, photographs, and photomicrographs of patients, specimens, and apparatus, which are used for following the progress of patients, for teaching, and for illustrating contributions to medical literature. A filing system allows quick collection of previously completed illustrations of a large variety of subjects. The Out-Patient Departments, the Diagnostic Clinic, and the Maternity Department have profited particularly from the work of the Institute in the ability that it provides to reconstruct early conditions.



PRESBYTERIAN HOSPITAL. (North Thirty-Ninth Street.)

The Research Division of the Institute, as is now generally known, has concerned itself with the problem of the chemistry of cell growth, and its researches in the subject of sulphur metabolism have directed attention from many quarters to the work of the Institute and the Hospital of which it is a part.

Presbyterian Hospital. The Presbyterian Hospital, incorporated in 1871 and opened the following year, was a happy product of the reunion, in 1869, of the two branches of the Presbyterian Church.

This Hospital, which never has had any restrictions as to race, creed, or color, has a consulting and major staff of about 170, and provides beds for

425 patients. The Out-Patient Department, with an annual visit-total of about 63,000, offers clinics in allergy, diseases of the heart, diabetes, thyroid and other conditions. A Child Health Clinic follows the Department for Prevention of Disease of the Children's Hospital, in emphasizing the modern doctrine of prevention.

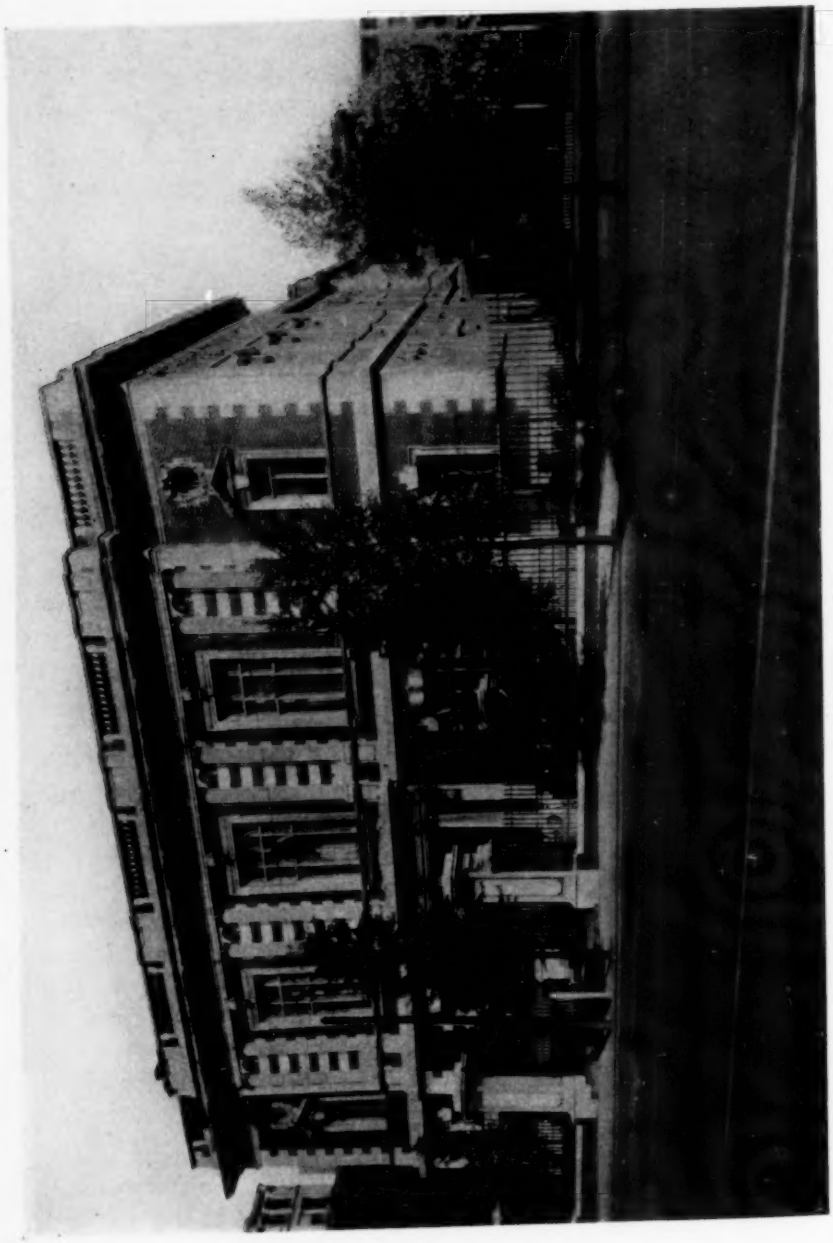
The physicians and interns, as in most hospitals, hold weekly clinical conferences in the laboratory for the discussion of unusual pathological conditions which arise in the routine of observation in the Hospital, and papers and other presentations are delivered at monthly scientific meetings. Recently a research committee has been instituted with a view to extending the general importance of the work done in the Hospital.

In general, coöperation between the Hospitals and the Medical Schools, which we have hinted at in speaking of the Graduate School of Medicine's "Pennsylvania Plan," is engaged in widely, and there can be little doubt that its ultimate effect is an advantageous one for all concerned.

It is to be expected that a city so rich in medical institutions should be rich alike in medical societies. About 50 of these advertise their meetings in the Weekly Roster published by the Philadelphia County Medical Society, and these do not constitute the entire list, of course. Of these, two must be mentioned. The largest in the city is the Philadelphia County Medical Society, at Twenty-First and Spruce Streets. Organized in 1849 under the presidency of Dr. Samuel Jackson, it has been from the beginning an extraordinarily active and effective medical police in the interests of the public welfare. Of late years it has become increasingly active in stimulating the interest of the younger physicians, the interns and medical students, by series of postgraduate seminars and round table discussions held in its building. The Weekly Roster which it publishes is an invaluable guide to the activities of the city's medical societies.

The oldest existing medical society in Philadelphia, and the most famous, is, of course, the College of Physicians, organized in 1787. Its present splendid home, which was built for it and to which it moved in 1909, houses one of the finest medical libraries in the world, both in size and in quality. Its collections of medical incunabula and other medical books of the greatest rarity are known in Europe as well as in this country. Over 200 of the incunabula have already been photostated by the Library's photostatic machine and are accessible to scholars in the reading room.* These collections and one of the most comprehensive files of medical periodicals in the country have resulted in making the College a court of first resource for those working in medical literature. The College holds monthly scientific meetings, except during the summer, often with distinguished guest speakers, and its Fellows have organized five Sections which likewise hold monthly meetings in the lecture halls of the College, which are used also by other medical societies in the city. The College, thus, is open six full days and many eve-

*A special exhibit of some of the rarest items has been arranged for the American College of Physicians and, likewise, arrangements have been made to introduce its members to the Mütter Museum and other treasures in the College building.



THE COLLEGE OF PHYSICIANS OF PHILADELPHIA. (19 South Twenty-Second Street.)

nings in the week, carrying on that " diffusion of medical knowledge " proposed as among its objects by one of its distinguished founders, Benjamin Rush.

Philadelphia's medical activities today include, further, the publication of 19 medical journals. Philadelphia is the home of five of the largest medical publishing houses in the country. Here are the headquarters of the American College of Physicians. Philadelphia today teaches medicine, practices medicine, thinks in terms of medical progress with the singular devotion which it inherits and passes on year by year. It is, in a spiritual sense at least, the medical center of America.

EDITORIAL

THE CERTIFICATION OF INTERNISTS AND THE PROPOSED EXAMINATIONS FOR FELLOWSHIP IN THE COLLEGE

THERE has been a well defined movement in American medicine towards the establishment of more definite criteria for the title of specialist. The ophthalmologists, the pediatricians, the neurologists and psychiatrists have either established special examining boards for certifying specialists in their respective fields or are in process of setting up machinery for so doing. The leadership in this movement has been taken by the American Medical Association, and its participation in the certifying process has recently been defined as follows:

ESSENTIALS FOR EXAMINING BOARDS IN SPECIALTIES

By the Council on Medical Education and Hospitals of the American Medical Association, Chicago

I. ORGANIZATION

1. A special examining board to be approved by the Council should represent a well recognized and distinct specialty of medicine.

2. It should be composed of representatives of the national organizations of that specialty including the related section of the American Medical Association.

3. It should be incorporated.

4. A special board should:

   (*a*) Determine whether candidates have received adequate preparation as defined by the board.

   (*b*) Provide a comprehensive test of the ability and fitness of such candidates.

   (*c*) Certify to the competence of those physicians who have satisfied the requirements of the board.

II. DEFINITION OF SPECIAL FIELDS

The following branches of medicine at present are recognized as suitable fields for the certification of specialists:

1. Internal Medicine
2. Surgery
3. Pediatrics
4. Obstetrics and Gynecology
5. Ophthalmology
6. Otolaryngology
7. Dermatology and Syphilology
8. Neurology and Psychiatry
9. Urology
10. Orthopedic Surgery
11. Radiology
12. Pathology

In the Milwaukee Session of the House of Delegates a resolution was adopted which read as follows:

"*Resolved*, That the Council on Medical Education and Hospitals is hereby authorized to express its approval of such special examining boards as conform to the standards of administration formulated by the Council; and be it further

"*Resolved*, That the Board of Trustees of the American Medical Association be urged to use the machinery of the American Medical Association, including the pub-

lication of its Directory, in furthering the work of such examining boards as may be accredited by the Council."

It is apparent, therefore, that the way is open for the American College of Physicians as the largest and most representative body of internists in this country to ally itself with the Section on the Practice of Medicine of the American Medical Association in setting up an examining board for the certification of specialists in internal medicine.

The decision of the College as to whether it should assume this responsibility is undoubtedly an important one both to the future of the College and to the success of the movement towards certification of specialists. The question deserves examination in some detail.

In the first place one may well ask what is the purpose of certifying specialists. The only valid answer would seem to be that such certification would constitute a natural and valuable extension of the laws of licensure of physicians. These laws are primarily for the purpose of ensuring to the public that those men who establish themselves in the community as practitioners of medicine have had adequate training to fit them for the responsibility they have assumed. It is inevitable that the public should some day demand that those physicians who assume the rôle of specialists in some field of medicine, with the definite further responsibilities that such a rôle entails, should likewise be forced to demonstrate adequate training and experience. Such a public demand has not yet become vocal but it would be justified. That this movement towards certification of specialists arises in the medical profession itself is excellent evidence that the members of that profession in this country are able to govern and to discipline themselves. The interest of all physicians in this attempt at self government may well be stimulated by the evidence available in another field of medical activity, medical economics, that when the profession fails to regulate its affairs wisely we are apt to suffer from laymen's attempts to rule us through unintelligent and unsympathetic laws.

If the medical profession of this country is to certificate its specialists in the near future, rather than await the day when legal licensure of specialists by State Boards will be forced upon us, it is evident that it is only by agreement of all in a common procedure, by just and impartial administration of the tests applied, and by education of the public in the meaning and value of the certification that success will be achieved. It seems apparent that the American Medical Association must be the coördinating body through which the work of the various Examining Boards is controlled and the results made public. Attempts of various associations, societies, academies or colleges in the separate specialties, no matter how powerful, to set up their own examining boards and claim public recognition for their members could end only in confusion and discredit to the profession. The question as to whether to take an active part in this movement under the leadership of the American Medical Association is one to be considered by each national organization in the special fields, but no plan for maintaining a competing

certifying board could be justified. On the other hand when a dominant national organization joins hands with the American Medical Association in this movement it might justly demand a controlling voice in determining the criteria for certification in its special field.

The question of the participation of the American College of Physicians in the certification of internists bears interesting relationships to the problems connected with the requirements for Fellowship. It so happens that there has been active discussion for some time among the Regents of the College, as may be seen in the minutes of their last meeting in Philadelphia, as to the advisability of requiring some form of examination for admission to Fellowship in the College. It is felt that the present methods of determining eligibility do not afford to the Committee on Credentials adequate information on which to base their decision, and a variety of more formal tests has been proposed. The opinion of the regents committee, appointed to consider this subject, has so far been divided both as to the advisability and the feasibility of instituting a system of practical and written examinations, which the candidate from the ranks of the Associates would be required to pass before the Fellowship was conferred. There has been discussion also as to the value to be assigned to postgraduate work, to original investigations, and to publications.

If the College should decide to play an active rôle in conjunction with the Section on the Practice of Medicine in certifying internists, no doubt such certification as an internist would become one of the prerequisites to application for Fellowship. Since all physicians desiring to be known as internists would be taking the examination of the certifying Board of Examiners the College would not be requiring an unusual test which might deter some desirable men from applying. It would also be in the more advantageous position of not receiving applications from those who had failed the examination of the certifying Board, rather than of being forced to reject a candidate because after applying he had been unsuccessful in passing the tests given by the College. The College would of course reserve its privilege of selecting from applicants who had passed the certifying examination only those who satisfied all other requirements for Fellowship.

The further requirements which should be met before a certified internist became eligible for Fellowship in the College would no doubt vary in the course of the years. The standard of requirements would progressively grow higher so that the title of Fellow would always mean not only adequate training and experience in internal medicine but especial distinction in professional ability, leadership and character. It might justly be expected that the young physician who adopted internal medicine as his career would be guided in his training by the requirements necessary to reach two successive goals, first the passing of his examination before the certifying Board and second his election as a Fellow of the American College of Physicians. In the interim years of his training he should find, as Associate member of the College, a valuable stimulus in the Annual Clinical Sessions. Perhaps in

time the Regents, Governors and Senior Fellows in each state may come to be the natural advisors and aids to the younger Associates who are seeking opportunities for further training in internal medicine. The College might well feel that no finer program could be adopted as its chief aim than to stimulate and assist young physicians in the study and practice of internal medicine, to ensure a fair and thorough method of their certification as internists, and to reward their further accomplishments by the bestowal of its Fellowship.

Desirable as such a program seems to be, it must be realized that the road to its establishment is beset with many practical difficulties.

The question of certification after examination must be so managed that the interests of those men already well established in practice must be safeguarded as must indeed the rights of those men already elected to Fellowship in the College. The character of the required training in internal medicine and the nature of the comprehensive examination for certification must be such as will not bar the man who is unable to finance many years of pure postgraduate study, and also such as will not permit a semblance of sound postgraduate study to pass for the reality. There is likely to be serious difficulty also in obtaining the proper personnel and facilities necessary for examining annually, or semi-annually the very large number of candidates who will apply.

It is obvious that before the American College of Physicians decides to take part in this movement it will be necessary to find a solution to these and many other practical difficulties. It is felt that from the Fellows and Associates of the College many valuable suggestions might come, as to the advisability of the undertaking, as to proper criteria for awarding certificates and as to feasible plans for the conduct of the examination. The advice of all members of the College will be welcomed. Communications addressed to the Editor will be placed before the Committee on Examinations. The whole question will be among the most important of those coming up for discussion before the governing bodies of the College at the coming sessions in Philadelphia.

REVIEWS

Definite Diagnosis in General Practise. By W. L. KITCHENS, M.D. 445 pages; 18 × 26 cm. W. B. Saunders Company, Philadelphia. 1934. Price, $10.00.

It is quite difficult to form an opinion about this very unusual book without a trial in practise. It is purely an index, with no text except eight pages of preface and instructions in the use of the volume. Consequently, its usefulness is almost as difficult to estimate as that of a card index file.

The volume is divided into two parts, the first of which lists, at the head of each page, a symptom of diagnostic importance. Under each symptom are listed those diseases in which the symptom occurs with a page number referring to the second section of the book. Altogether, 506 symptoms are listed. A sub-index, heading this section, serves as a guide and cross-index.

The second section is made up of 407 pages, each devoted to the symptomatology of a disease. Each symptom listed is numbered, the number referring to a page in the first section headed by that particular symptom.

Thus, page 140, in part one, is headed "Dyspnea". Listed here are 65 diseases or pathological states in which dyspnea may occur, with page numbers indicating the section in part two listing the symptomatology of each of these diseases. Four hundred and seven diseases are listed in all.

The author states in his introduction that this book cannot take the place of a text. This is, of course, quite true. Descriptions of neither diseases nor symptoms are given, and to pass judgment on a patient without confirming the book's suggestions appears difficult or impossible. No attempt is made to classify symptoms as to their major or minor importance in any disease, nor to indicate whether symptoms are due to the disease itself or a complication.

Certain striking omissions are noted. Cyanosis is not mentioned as occurring in pulmonary embolism or pulmonary edema. Fever, pericarditis, and leukocytosis are not listed under coronary thrombosis. The author has made some provision for these and other omissions, as there is ample space on each page for the physician's own list of additional symptoms and diseases.

This book should be of use in differential diagnosis, and as an easily available symptom list in teaching. It is doubtful, however, if it will make diagnosis as simple, easy, and definite as stated on the jacket. T. N. C.

Synopsis of Genito-Urinary Diseases. By AUSTIN I. DODSON, M.D. 275 pages. C. V. Mosby Co., St. Louis. 1934. Price, $3.00.

This small synopsis of 265 pages of text is somewhat of a departure from the stereotyped textbooks on genito-urinary diseases in that it does not take up the genito-urinary system in the order of its anatomical arrangement but rather emphasizes the attack of various diseases on the structures in proportion to their common occurrence. It is illustrated by eight photographs and 103 descriptive illustrations, the author having availed himself of the use of some of the best drawings of other books on genito-urinary diseases.

Chapter 2 is distinctive in that it shows drawings and photographs of the common instruments and procedures used in diagnosing and treating infections in the lower urinary tract. Although in this small book infections of necessity have been dealt with in a brief manner, there are over two pages devoted to the treatment of gonorrheal urethritis. This is excellent because this book will be read by many general practitioners and here is an outline to be observed in the management of this type of case.

In Chapter 10 the newer views of stone formation are sketched and the significance of associated infection is explained. The author says in the chapter on Prostatism that "The excellent results obtained in prostatic surgery are due chiefly to the careful preoperative treatment."

J. H. T.

What We Are and Why. By LAURENCE H. MAYERS, M.D., and ARTHUR D. WELTON. 340 pages; 14.5 × 21 cm. Dodd, Mead and Company, Inc., New York. 1933. Price, $3.00.

The title and subtitle of this interesting little book indicate its general trend and the contents confirm the indication that there is, in the authors' opinion, only one important determinant of human conduct or of dispositional traits.

The authors' main thesis is that the infectious diseases of childhood, measles, whooping cough, scarlet fever, diphtheria and especially mumps, are lamentably frequent, are usually neglected and often exert a harmful effect on the endocrine glands, with the result that the unfortunate victim must go through life handicapped by physical disabilities, by personality defects, or by both. The authors state in the preface that it is their hope that their illustrative cases may have some influence in warding off from gland victims the opprobrium which they so often receive.

The book, designed for the layman, is attractively written with a breezy, easily readable style. The case reports are dramatically interesting instead of being dull and tedious and they are illustrated by excellent photographs. Nevertheless, a conservative reviewer cannot recommend, except for its entertaining qualities, a book so untrammelled by scientific rules. Many of its most entertaining features are based upon analogy or fancy; indeed, on page 217, the authors poke gentle fun at physiologists, pathologists and other punctilious scientists who are bound by hard rules of scientific evidence, and again on page 226, they say, "None of these statements coincides with the scientific observations of the physiologists."

Lacking these handicaps the book abounds in entertaining and sweeping statements, as for example, on page 232, "Naturally the experiments have been extensive and naturally there is variation in results and opinions but there is none in the belief that in the pituitary is found the center and stimulus of activity, both physical and mental." Again on page 195, "It is not our purpose to account for flagpole sitting or to try to classify it as a form of self-expression. It is mentioned only as an example of emotional eccentricity, founded in exhibitionism, which is infantilism, which is a result of glandular derangement."

The book presents cleverly and attractively the viewpoints of psychologists who have given endocrinology a joyous and enthusiastic welcome.

T. P. S.

Arteriosclerosis; A Survey of the Problem. Edited by EDMUND V. COWDRY. xvii + 617 pages; 16.5 × 24 cm. The Macmillan Co., New York. Price, $5.00.

This volume presents a survey of the problem of arteriosclerosis. There are, including an Introduction by Ludwig Aschoff and a Summary by Alfred E. Cohn, twenty-three contributors. The book has twenty-one chapters, in each of which the problem is approached from a different aspect. It is attacked from the historic, the physiologic, the chemic, the statistical, the pathologic, the etiologic, the clinical and other points of view. It is stated that the contributors have had three objects clearly in mind: "To determine the data concerning arteriosclerosis which can be regarded as established and their relation to one another; to discover and definitely formulate the principal problems awaiting solution; and to suggest the best means of attacking them." The reviewer considers that this volume is a valuable step in attaining such objectives. It is an exhaustive compendium of present knowledge relating to the

subject, and many suggestions are offered for the furtherance of that knowledge. The various sections are furthermore surprisingly uniformly well written and interesting. There are included extensive references to the literature extant. The clinician will find this volume an excellent summary of present day knowledge of arteriosclerosis.

W. S. L., Jr.

Hygiene for Freshmen. By Alfred Worcester, A.M., M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. viii + 154 pages; 15 × 25 cm. Charles C. Thomas, Baltimore. 1934. Price, $1.50.

This is a brief and rather informal textbook used in the Freshman course in Hygiene at Harvard University. The course, as described, is a weekly series of lectures throughout the first semester, and the textbook is apparently a summary of the lectures as they are delivered to the students.

In order to overcome the lack of a preliminary course in biology, the author has presented a clear and interesting summary of the essential biological and physiological processes, and correlated them with everyday life and habits. Following this plan, the student is introduced, by short but comprehensive chapters, to biology and embryology, the circulation, glands of internal and external secretion, nutrition, digestion, muscular physiology and the nervous system.

The chapter on mental hygiene should be especially valuable to the college freshman, discussing as it does, the new responsibilities, problems and conflicts that beset the freshman student, and the danger signals that indicate the necessity of psychiatric help. The discussion of reproduction and physiology of the sex organs is sound and well written, and should be of help to the late adolescent entering a difficult period of life. The course closes with chapters on prevention of disease and immunity.

In general, this book gives one the opinion that the average student, and especially the student in medical school, should be benefited by becoming acquainted with it, and by application of its principles.

T. N. C.

PROGRAM

NINETEENTH ANNUAL CLINICAL SESSION AMERICAN COLLEGE OF PHYSICIANS PHILADELPHIA, PA.

April 29–May 3, 1935

GENERAL SESSIONS

Jonathan C. Meakins, President

PHILADELPHIA COMMITTEES

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Alfred Stengel, Chairman

T. Grier Miller
Ross V. Patterson
O. H. Perry Pepper
George Morris Piersol
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William D. Stroud
Pennsylvania Hospital
Edward Weiss
Temple University Hospital
G. Harlan Wells
Hahnemann Hospital
Edward B. Krumbhaar
University of Pennsylvania School of Medicine
Charles C. Wolferth
Hospital of the University of Pennsylvania

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Edward Weiss

COMMITTEE ON ENTERTAINMENT

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COMMITTEE ON ENTERTAINMENT OF VISITING WOMEN

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Mrs. Edward Bortz
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Mrs. William D. Stroud
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Mrs. H. B. Wilmer
Mrs. Charles C. Wolferth

DIRECTORY

General Headquarters.....Municipal Auditorium, 34th St. below Spruce
Hotel Headquarters.....The Benjamin Franklin Hotel, 9th & Chestnut Sts.
General Registration.....Exhibition Floor, Municipal Auditorium
Board of Regents.....Room 200, Lobby, Municipal Auditorium
Board of Governors.....Room 200, Lobby, Municipal Auditorium
Executive Secretary's Office.....Room 103, Exhibition Floor, Municipal Auditorium
Publicity, Press Room.....Exhibition Floor, Municipal Auditorium
Technical Exhibits.....Exhibition Floor, Municipal Auditorium
General Scientific Sessions.....Arena, Municipal Auditorium
Morning Lectures.....Exhibition Floor, Municipal Auditorium
Convocation.....Ballroom, Benjamin Franklin Hotel
Annual Banquet.....Ballroom, Benjamin Franklin Hotel
Ladies Registration and Headquarters.....Franklin Room, Mezzanine Floor, Benjamin Franklin Hotel

WHO MAY REGISTER—

(*a*) All members of the American College of Physicians in good standing for 1935 (dues, if not paid previously, may be paid at the Registration Bureau).

(*b*) All newly elected members.

(*c*) Members of the College of Physicians of Philadelphia and of the Philadelphia County Medical Society, without registration fee, upon presentation of their 1935 membership cards; exhibits, general sessions and for the special morning lectures.

(*d*) Senior medical students pursuing courses at the University of Pennsylvania School of Medicine, Jefferson Medical College of Philadelphia, Woman's Medical College of Pennsylvania, Hahnemann Medical School and Hospital, and Temple University School of Medicine, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions; exhibits, general sessions and for the special morning lectures.

(*e*) House Officers of the hospitals participating in the program, upon presentation of proper identification; exhibits, general sessions and for the special morning lectures.

(*f*) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

(*g*) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the "Annals of Internal Medicine" (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU.—Temporary Registration Bureau will be open on the mezzanine floor of the Benjamin Franklin Hotel on Sunday afternoon and evening, April 28. The permanent Registration Bureau will be located at the entrance to the Exhibition Room of the Municipal Auditorium. Hours: 8:30 A.M. to 6:00 P.M., daily, April 29–May 3.

REGISTRATION BLANKS FOR SPECIAL MORNING LECTURES, AND FOR ALL CLINICS AND DEMONSTRATIONS will be sent with the formal program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

CHANGES OF ADDRESS, errors in names, etc., should be reported at the Registration Bureau.

THE CASHIER'S DESK at the Registration Bureau will receive payment of dues still delinquent, and accept orders for Banquet tickets, the College Key, the framed Fellowship Pledge, the Fellowship Certificate Frame and subscriptions to the "Annals of Internal Medicine."

BULLETIN BOARD FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau in the Municipal Auditorium.

TRANSPORTATION.—Round trip tickets may be procured on the basis of one and one-third of the current one-way first class fares, with minimum excursion fare of $1.00 for the round trip, upon presentation of identification certificates to be procured from the Executive Secretary of the American College of Physicians. The reduced fares apply for physicians and dependent members of their families.

Members are privileged to make the going journey by one route, and return by another route. The fare for children of five and under twelve years of age will be one-half of the round trip fare for adults; children under five years of age free when accompanied by parents or guardian. Stop-overs will be allowed at all stations within final limit on either going or return trip, or both, upon application to conductors.

Before purchasing tickets, members must secure from the Executive Secretary an Identification Certificate, to entitle them to the reduced fares.

In general, tickets will be sold from April 17 to May 1, depending upon the relative distance from Philadelphia, with a return limit of thirty days in addition to date of sale.

All tickets must be validated by a special railroad agent at the Philadelphia headquarters in the Municipal Auditorium from April 29–May 3.

SPECIAL TRAIN SERVICE

If a sufficient number of members apply, the following special trains will be operated to and from the Philadelphia Session. Apply to the Executive Secretary of the College, or to the ticket agent of one of the participating roads, for further information.

Special Train from Chicago

Baltimore & Ohio R. R.

(Going)

Lv. Chicago (B. & O. R. R.)	10:00 A.M.	C.T.—April 28
Lv. Chicago (63rd Street Station)	10:25 A.M.	C.T.—April 28
Lv. South Chicago	10:45 A.M.	C.T.—April 28
Lv. Gary, Ind.	11:02 A.M.	C.T.—April 28
Ar. Garrett, Ind.	1:19 P.M.	C.T.—April 28
Lv. Garrett, Ind.	2:22 P.M.	E.T.—April 28
Lv. Defiance	3:17 P.M.	E.T.—April 28
Lv. Deshler	3:54 P.M.	E.T.—April 28
Lv. Cleveland (B. & O. R. R.)	2:50 P.M.	E.T.—April 28
Ar. Akron (Union Station)	4:25 P.M.	E.T.—April 28
Lv. Akron	7:03 P.M.	E.T.—April 28
Lv. Youngstown	8:22 P.M.	E.T.—April 28
Lv. Newcastle, Pa.	8:54 P.M.	E.T.—April 28
Lv. Pittsburgh, Pa. (P. & L. E. Smithfield Station)	10:25 P.M.	E.T.—April 28
Lv. McKeesport, Pa.	10:59 P.M.	E.T.—April 28
Lv. Connellsville, Pa.	12:03 A.M.	E.T.—April 29
Ar. Philadelphia	8:53 A.M.	E.T.—April 29

Special Service from St. Louis

Lv. St. Louis (B. & O. R. R.)	9:15 A.M.	—April 28
Lv. Vincennes	12:20 P.M.	—April 28
Lv. Mitchell, Ind.	1:45 P.M.	—April 28
Lv. Louisville (B. & O. R. R.)	1:25 P.M.	—April 28
Ar. Cincinnati	5:45 P.M.	—April 28
Lv. Cincinnati (B. & O. R. R.)	6:00 P.M.	—April 28
Lv. Winton Place	6:10 P.M.	—April 28
Lv. Oakley, Ohio	6:21 P.M.	—April 28
Lv. Chillicothe	8:20 P.M.	—April 28
Lv. Parkersburg, W. Va. (Sixth St. Station)	10:35 P.M.	—April 28
Lv. Clarksburg	12:45 A.M.	—April 29
Lv. Washington, D. C.	8:00 A.M.	—April 29
Lv. Baltimore, Md. (Camden Station)	8:44 A.M.	—April 29
Lv. Baltimore, Md. (Mt. Royal Station)	8:50 A.M.	—April 29
Ar. Philadelphia	10:48 A.M.	—April 29

In view of the uncertainty at this time as to those who may desire to return in group parties, it is thought advisable to wait until after arrival at the convention to ascertain what special services for the return trip will be required.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5:00 P.M., Thursday, May 2, immediately following the general scientific program

of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary and the induction to office of the new President, Dr. James Alex. Miller, New York, New York.

BOARD AND COMMITTEE MEETINGS.—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

COMMITTEE ON CREDENTIALS

Sunday, April 28, 10:00 A.M.....Room 103, Exhibition Floor, Municipal Auditorium

BOARD OF REGENTS

Room 200, Lobby, Municipal Auditorium

Sunday, April 28, 2:00 P.M.
Tuesday, April 30, 12:00 M.*
Friday, May 3, 12:00 M.*

BOARD OF GOVERNORS

Room 200, Lobby, Municipal Auditorium

Monday, April 29, 5:00 P.M.
Wednesday, May 1, 12:00 M.*

* Buffet luncheon served.

SPECIAL FEATURES

Monday, April 29, 1935

THE ANNUAL SMOKER.—Immediately following the scientific program, at ten-thirty o'clock, Monday evening, in the main Ballroom of the Benjamin Franklin Hotel. An unusual program of entertainment and music will be given by the Orpheus Club of Philadelphia.

Among the features will be Dr. Alberto Bimboni and Mr. Ellis Hammond, piano duo; Mr. John Ott and Mr. Albert Zimmerman, piano and vocal song hits of the day; Mr. H. Tatnall Brown, Jr., impersonations; and many other interesting features.

Wednesday, May 1, 1935

CONVOCATION OF THE COLLEGE.—8:15 P.M., Ballroom, Benjamin Franklin Hotel. All Masters and Fellows of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in the Betsy Ross Room, mezzanine floor, Benjamin Franklin Hotel, at seven-thirty o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the ballroom to which they will be conducted by the Convocation marshall promptly at 8:15. As this is the most formal meeting of the College, it is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally, and to such of the general public as may be interested.

Following the Convocation ceremony, the President will present the John Phillips Memorial Medal for 1934–35. Thereafter will follow the Convocational Oration, "The Thyroid Stimulating Hormone of the Anterior Pituitary Gland," by Dr. Leo Loeb, Professor of Pathology, Washington University, St. Louis.

The President, Dr. Jonathan C. Meakins, of Montreal, Canada, will then deliver the annual presidential address to the Masters, Fellows and Associates of the College.

The Presidential Reception in the Betsy Ross Room, mezzanine floor, will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception. All members and guests are invited to remain for dancing in the Grand Ballroom following the Reception.

THURSDAY, MAY 2, 1935

THE ANNUAL BANQUET OF THE COLLEGE will be held at the Benjamin Franklin Hotel at 8:00 P.M. All members of the College and its Officers, physicians of Philadelphia and visitors attending the Session, with their families, are invited to be present. Consult the formal program to be printed later for announcements concerning the toastmaster and principal speakers.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The following program has been arranged with a view also to leave ample time for sight-seeing, shopping and recreation. Complete lists of points of interest, principal shops, concerts and lectures will be issued by the local committee.

The Franklin Room, Mezzanine Floor of the Benjamin Franklin Hotel, will be the headquarters for the visiting ladies.

MONDAY, APRIL 29, 1935

Morning: Registration (Franklin Room, Benjamin Franklin Hotel).

Afternoon: 2:00 P.M. Sight-seeing trip of Philadelphia and Fairmount Park. Tea at Strawberry Mansion, one of the old historical houses. Busses will leave from and return to the Benjamin Franklin Hotel.

Evening: 8:30 P.M. Lecture at the Planetarium, Franklin Institute, 20th St. & The Parkway.

10:30 P.M. Men's Smoker, Ballroom, Benjamin Franklin Hotel.

TUESDAY, APRIL 30, 1935

Afternoon: 1:30 P.M. Trip to Valley Forge. Visit Rock Garden of Mr. & Mrs. Richard Haughton, Paoli. Tea at "Summerhill," Newtown Square, Residence of Mrs. Alfred Stengel.

Busses will leave from and return to the Benjamin Franklin Hotel.

Evening: The theatre, optional.

WEDNESDAY, MAY 1, 1935

Afternoon: 1:00 P.M. As guests of the local committee, Luncheon at the Philadelphia Country Club, followed by golf or bridge for those who care to play.

Busses will leave the Benjamin Franklin Hotel at 12:30 P.M.

Evening: 8:15 P.M. Annual Convocation, Ballroom, Benjamin Franklin Hotel. All ladies are cordially invited.

THURSDAY, MAY 2, 1935

Afternoon: 1:30 P.M. As guests of the local committee, visit the green houses of Mr. & Mrs. Pierre duPont at "Longwood", Kennett Square, Pa.

Cars will leave the Benjamin Franklin Hotel promptly.

Evening: 8:00 P.M. Annual Banquet, Ballroom, Benjamin Franklin Hotel.

THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY, affiliated with the University of Pennsylvania, and located on the University campus at Thirty-

Sixth and Spruce Streets, will be open to Fellows of the College daily from 9:00 to 5:00. Dr. Milton J. Greenman, Director of the Institute, has kindly offered to arrange demonstrations of the work of the Institute.

The work of the Institute is devoted to researches in neurology, genetics and animal behavior, and its laboratories will be open to the visits of our members.

THE UNIVERSITY MUSEUM, an institution devoted to the study of the history of mankind, particularly as represented by the remains of ancient civilizations, is open to all visitors daily, except Monday, from 10 to 5. Located at 34th and Spruce Streets within a block of the Municipal Auditorium, the Museum will be easily accessible to all attending the College meetings.

The Museum contains collections obtained through various expeditions to many parts of the world, and is one of the outstanding Archeological Museums of the world.

THE HALL AND LIBRARY OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA (22nd Street between Chestnut and Market Streets) will be open to visits and inspection by those attending the meeting of the American College of Physicians, daily from 10 to 5.

Special displays of rare medical publications and medals, portraits and other objects of medical interest will be arranged for this occasion.

The Librarian, Mr. McDaniel, and members of the Library Committee will be at the Library to receive visitors and explain the displays.

THE LIBRARY OF THE PENNSYLVANIA HOSPITAL is the oldest medical library in the United States. It possesses many books of great historical interest and also other objects which date back to the earliest days of this very old hospital. Exhibits in the Library will be arranged by Dr. Francis R. Packard and the Library will be open to members of the College each day during the clinical sessions from 9:00 A.M. to 1:00 P.M.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the Exhibition Floor of the Municipal Auditorium.

Exhibits consisting of medical literature and texts, pharmaceutical products, apparatus and appliances, special foods, etc., will be shown by the leading publishers and manufacturers. The leading medical placement bureaus will also be among the exhibitors this year. There will be many new exhibits not heretofore shown before the American College of Physicians.

These exhibits afford an opportunity for physicians to examine the latest literature and the newest products in the field of medicine generally; their educational value should not be overlooked. Every attendant at the Session is urged to visit each of the booths, for he will certainly find something new, interesting and scientifically valuable. Intermissions in the general program have been arranged from Monday to Friday, inclusive, for the purpose of providing a definite time for the inspection of exhibits.

GENERAL SESSIONS

The selection of the program for the General Sessions is a task of no small dimenmensions. The response of the Fellows and friends of the College was most gratifying; in fact, it could almost be said embarrassing, as the number of contributions offered was several times greater than could possibly be accommodated in the comparatively short time at our disposal. No attempt was made to arrange symposia although, as would be expected, many of the contributions lend themselves to an arrangement for viewing certain problems from different angles.

Fundamental aspects of physiology and biochemistry have been given a place beside the more practical problems of medicine. This serves the good purpose of throwing into relief the future trends of investigation towards the elucidation of our many difficulties.

The *Diseases of Cardiovascular System* are principally discussed from the point of view of the peripheral circulation as distinct from the heart alone. The subject of vascular disease as influenced by other systemic disorders is particularly viewed from the standpoint of the diabetic, while at the same time the latest advances in carbohydrate metabolism are considered by one of the outstanding workers in this field.

Neurology has a place in the program not only in diseases of common occurrence and of great interest to the internist, but also there will be a communication dealing with the most fundamental modern aspects of neurologic physiology.

Endocrinology will be discussed from a number of aspects of interest both to the physician and the experimentalist. The most recent concepts of endocrine balance and unbalance and interlocking control by anti-hormone action are discussed by one of the greatest authorities and the pioneer in this subject. Other phases of endocrinology are also considered.

Diseases of the Lungs are covered from a number of angles. The increasing interest in the newer concepts of chronic pulmonary diseases of a non-tuberculous nature is catered to by a number of essayists. Other phases of this subject are reviewed and the latest results critically analyzed and placed before the Fellows and guests by those fully qualified for such an authoritative review. Of particular interest is a communication dealing with the processes of healing in collapse therapy.

Hematology is considered rather from the standpoint of taking stock of the present state of our knowledge of such important disorders of the hematopoietic system as the anemias in pregnancy, aplastic and agranulocytic angina. Much confusion reigns in certain phases of these subjects and it is intended that as far as possible order may be restored.

The papers on *Gastro-enterology* are chiefly concerned with the liver both from the experimental and clinical aspects. The mysteries of hepatic cirrhosis have been investigated. This subject was before the College some years ago but the present communications carry the subject some steps further in its elucidation.

Certain phases of *Infectious Diseases* and *Immunology* are dealt with and original and stimulating concepts are put forward.

The *Convocational Oration* will be delivered on Wednesday evening by Professor Leo Loeb, of St. Louis. Professor Loeb during a period of approximately forty years has contributed to many fields of general and experimental pathology. His researches have had a profound effect upon Medical Science and in particular his work on the thyroid stimulating hormone of the anterior hypophysis, which will be the subject of his address.

GENERAL HEADQUARTERS

MUNICIPAL AUDITORIUM

34th Street below Spruce

Registration headquarters, railroad office, information bureau, exhibits and the general assembly hall are all located here.

HOTEL HEADQUARTERS

BENJAMIN FRANKLIN HOTEL

9th and Chestnut Sts.

The Benjamin Franklin Hotel will be the headquarters hotel for Officers, Regents, and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Reservations that the Benjamin Franklin Hotel cannot fill will be referred immediately to some other hotel conveniently local.

Apply directly for reservations to the hotel of your choice. Physicians are requested to mention specifically the fact that reservations are being made in connection with the Clinical Session of the American College of Physicians.

LIST OF PHILADELPHIA HOTELS

Name and Location	No. of Rooms	RATES PER DAY				
		ROOM—ONE PERSON		ROOM—TWO PERSONS		SUITES
		With Bath	Without Bath	With Bath	Without Bath	
Benjamin Franklin, 9th and Chestnut	1200	$3.50–5.00	.....	$5.00–8.00	.....	$ 8.00–20.00
Adelphia, 13th and Chestnut	400	3.50 up	.....	5.00–8.00	.....	10.00
Barclay, Rittenhouse Square E	634	4.00 up	.....	6.00 up	.....	10.00
Bellevue-Stratford, Broad and Walnut	800	3.50–5.00	2.50–3.50	5.00–9.00	4.00–6.00	15.00–20.00
Broadwood, Broad and Wood	200	2.00 up	.....	4.00 up	.....	.....
Colonial, 11th and Spruce	100	2.50 up	1.50–2.00	3.50–5.00	2.00–3.00	5.50–8.00
Drake, 1512 Spruce	150	4.00 up	.....	6.00 up	.....	10.00–12.00
Lorraine, Broad and Fairmount	300	2.50–3.50	2.00–2.50	5.00–6.00	3.50–4.00	5.00–8.00
McAlpin, 10th at Chestnut	116	2.00 up	1.50	4.00 up	3.00–3.50	.....
Normandie, 36th and Chestnut	234	2.50–3.00	2.00	3.50–4.00	3.00	5.00–7.00
Pennsylvania, 39th and Chestnut	600	2.50–5.00	.....	4.00–8.00	.....	8.00–15.00
Ritz-Carlton, Broad and Walnut	190	4.00–7.00	.....	7.00–9.00	.....	10.00
Robert Morris, 17th and Arch and Pkwy	208	2.50–4.00	.....	4.00–6.00	.....	.....
Roosevelt, 23rd and Walnut	150	2.50	.....	4.00	.....	5.00–8.00
St. James, 13th and Walnut	178	2.50–3.50	2.00	4.00–6.00	3.50	5.00–8.00
Stephen Girard, 2027 Chestnut	100	2.50–3.50	.....	4.00–6.00	.....	6.00–8.00
Sylvania, Juniper and Locust	400	3.00	.....	5.00*	.....	12.00 up
Walnut Park Plaza, 63d and Walnut	520	3.00	.....	4.00–5.00	.....	5.00–10.00
Walton, Broad and Locust	350	2.50–4.50	2.00–2.50	4.00–7.00	3.50–4.00	8.00–12.00
Warwick, 17th and Locust	900	4.00	.....	6.00	.....	10.00–15.00
Y.W.C.A.-Lincoln Hotel, 1222 Locust	90	2.50	1.25–2.00	4.00	3.00	.....

* Extra large triple room, 3 beds, with bath or shower, $6.00

OUTLINE OF SESSION

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 29	April 30	May 1	May 2	May 3
9:00 A.M. to 12:00 M.	Morning free. Registration, Exhibits, etc.	Special Morning Lectures / 1st Clinical Session	Special Morning Lectures / 2nd Clinical Session	Special Morning Lectures / 3rd Clinical Session	Special Morning Lectures / 4th Clinical Session
12:00 M. to 2:00 P.M.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:00 P.M. to 5:30 P.M.	**1st General Session**	**3rd General Session**	**5th General Session**	**6th General Session** Annual Business Meeting	**7th General Session**
5:30 P.M. to 8:00 P.M.	Dinner	Dinner	Dinner		
8:00 P.M. to 11:00 P.M.	**2nd General Session** followed by Smoker	**4th General Session**	Convocation, followed by President's Reception and Dance	ANNUAL BANQUET	

GENERAL SESSIONS

Philadelphia, Pa.—April 29–May 3, 1935

OPENING GENERAL SESSION

Monday Afternoon, April 29, 1935

P.M.

2:00 Addresses of Welcome:
Alfred Stengel, General Chairman of the Nineteenth Annual Clinical Session.
J. Norman Henry, Director of Public Health, City of Philadelphia.
Seth A. Brumm, President, Philadelphia County Medical Society.
Response to Addresses of Welcome:
Jonathan C. Meakins, President of the American College of Physicians.

2:30 The Mechanism of the Lesions of Multiple Sclerosis.
Tracy J. Putnam, Boston, Mass.

2:55 The Nervous Control of the Heart and Blood Vessels.
Detlev W. Bronk, Philadelphia, Pa.

3:20 Creatine Metabolism in Muscle Disease.
A. T. Milhorat and H. G. Wolff, New York, N. Y.

3:40 The Diagnosis and Treatment of Myasthenia Gravis.
Walter M. Boothby, Rochester, Minn.

4:05 INTERMISSION.

4:25 The Experimental Effects of Anterior Pituitary Hormones on Cranial Growth, and their Significance in Clinical Medicine.
Hector Mortimer, Montreal, Que.

4:50 Personality and the Endocrines: A Quantitative Study in 1400 Necropsies.
Walter Freeman, Washington, D. C.

5:10 The Fundamental Mechanism in the Production of Chronic Lymphatic Leukemia.
B. K. Wiseman and C. V. Moore, Columbus, Ohio.

5:30 ADJOURNMENT.

SECOND GENERAL SESSION

Monday Evening, April 29, 1935

Presiding Officer

James B. Herrick, Chicago, Ill.

P.M.

8:00 Studies on the Increased Metabolism in Hyperthyroidism.
E. Cowles Andrus and Donald McEachern, Baltimore, Md.

8:20 Internal or Visceral Myxedema.
Hans Lisser, San Francisco, Calif.

8:40 Dissociation of the Thyroid from the Sympathetic Nervous System in the Treatment of Angina Pectoris and Congestive Heart Failure.
James Alex. Lyon and Edmund Horgan, Washington, D.C.

9:05 Fatal Diabetic Coma with Acute Renal Failure.
Maynard E. Holmes, Syracuse, N. Y.
9:25 Etiology and Sequelae of Acute Glomerular Nephritis: A Study of 136 Cases.
Francis D. Murphy, Milwaukee, Wis.
9:45 Growth and Development of Function in Blood Vessels and Lymphatics. (Motion Picture.)
E. R. Clark, Philadelphia, Pa.
10:05 ADJOURNMENT.

10:30 o'Clock

SMOKER

Ballroom, Benjamin Franklin Hotel

The Orpheus Club of Philadelphia will present a program of entertainment of unusual merit.

THIRD GENERAL SESSION

Tuesday Afternoon, April 30, 1935

Presiding Officer

C. Hartwell Cocke, Asheville, N. C.

P.M.
2:00 Etiology of the Pulmonary Fibroses and Medico-Legal Aspects of Pneumoconiosis.
Wm. S. McCann, Rochester, N. Y.
2:20 The Experimental and Pathological Aspects of Silicosis.
Dudley Irwin, Toronto, Ont.
2:40 Basic Points in X-Ray Studies of Lung Anatomy and Pathology.
John H. Skavlem and Kennon Dunham, Cincinnati, Ohio.
3:00 Pulmonary Fibrosis and Emphysema.
James Alex. Miller, New York, N. Y.
3:20 Oleothorax—Clinical and Experimental.
John N. Hayes, Saranac Lake, N. Y.
3:40 INTERMISSION.
4:00 Healing Mechanisms in Collapse Therapy.
Max Pinner, Tucson, Ariz.
4:20 The Present Status of Artificial Pneumothorax in the Treatment of Lobar Pneumonia.
S. S. Leopold and L. M. Lieberman, Philadelphia, Pa.
4:40 The Use of Helium as a New Therapeutic Gas in the Treatment of Asthma.
Alvan L. Barach, New York, N. Y.
5:00 Accessory Sinus Infection: Its Relation to Mastoid and Lung Infections.
W. F. Manges, Philadelphia, Pa.
5:20 A Proposed Method of Evaluation of the Therapeutic Potency of Substances Effective in Pernicious Anemia and Its Application to Treatment.
Bernard M. Jacobson and Cyrus Fiske, Boston, Mass.
5:35 ADJOURNMENT.

FOURTH GENERAL SESSION

Tuesday Evening, April 30, 1935

Presiding Officer

Francis M. Pottenger, Monrovia, Calif.

P.M.

8:00 Further Studies on the Thymus and Pineal Glands. (Motion Picture.)
L. G. Rowntree, Philadelphia, Pa.

8:25 Recent Work on Anti-Hormones.
J. B. Collip, Montreal, Que.

8:50 Medullary Tumors of the Adrenal Glands.
M. C. Pincoffs, Baltimore, Md.

9:10 Hypothyroidism: A Common Symptom.
Roger I. Lee, Boston, Mass.

9:30 Correlations of the Endocrine System.
David L. Thomson, Montreal, Que.

10:00 ADJOURNMENT.

FIFTH GENERAL SESSION

Wednesday Afternoon, May 1, 1935

Presiding Officer

John H. Musser, New Orleans, La.

P.M.

2:00 The Relationship of the Flat Chest to Physical and Mental Development. (Illustrated by Slides and Motion Pictures.)
S. A. Weisman, Minneapolis, Minn.

2:30 Immunological Application of Placental Extracts.
Charles F. McKhann, Boston, Mass.

2:50 Experimental Studies Relating Vitamin "C" Deficiency to Rheumatic Fever and Rheumatoid Arthritis.
James F. Rinehart, San Francisco, Calif.

3:15 Further Observations on the Treatment of Chronic Rheumatoid Arthritis with Streptococcal Vaccine.
Charles W. Wainwright, Baltimore, Md.

3:30 INTERMISSION.

3:50 Von Gierke's Glycogen Disease.
L. M. Lindsay, Montreal, Que.

4:10 Alterations in Hepatic Function Produced by Experimental Liver Lesions.
Jesse L. Bollman, Rochester, Minn.

4:30 Clinical Observations on Some Phenomena Associated with Chronic Liver Damage.
A. M. Snell, Rochester, Minn.

4:50 An Instance of Possible Cirrhosis of the Liver Induced by a Hair Tonic Containing Carbon-tetrachloride.
B. B. Vincent Lyon, Philadelphia, Pa.

5:10 Incidence of Crateriform Ulcers of the Duodenum: A Roentgenologic and Pathologic Study.
B. R. Kirklin and H. A. Burch, Rochester, Minn.
5:30 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, May 1, 1935

8:15 o'Clock

Ballroom, Benjamin Franklin Hotel

The general profession and the general public are cordially invited. No special admission tickets will be required.

1. Convocation Ceremony.
2. Presentation of the John Phillips Memorial Medal.
3. Convocational Oration: "The Thyroid Stimulating Hormone of the Anterior Pituitary Gland."
   Leo Loeb, Professor of Pathology, Washington University, St. Louis, Mo.
4. Presidential Address.
   Jonathan C. Meakins, Montreal, Que.

Presidential Reception

Betsy Ross Room, Benjamin Franklin Hotel

The Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

Dancing

SIXTH GENERAL SESSION

Thursday Afternoon, May 2, 1935

Presiding Officer

James Alex. Miller, New York, N. Y.

P.M.

2:00 Lymphedema of the Extremities: Etiology, Classification and Treatment.
E. V. Allen and R. K. Ghormley, Rochester, Minn.
2:20 Cardiac Output in Common Clinical Conditions, and the Diagnosis of Myocardial Insufficiency by Cardiac Output Methods.
Isaac Starr, Jr., and C. J. Gamble, Philadelphia, Pa.
2:40 Studies on Cardiac Hemodynamics in Hypertension.
J. Murray Kinsman, Louisville, Ky.

3:05 Acute Cor Pulmonale.
Paul D. White, Boston, Mass.
3:20 Etiology and Prevention of Anemia in Pregnancy.
Maurice B. Strauss, Boston, Mass.
3:40 INTERMISSION.
4:00 Clinical Course and Pathological Changes in Aplastic Anemia.
C. P. Rhoads, New York, N. Y.
4:20 Diagnosis and Treatment of Agranulocytic Angina.
Henry Jackson, Jr., Boston, Mass.
4:45 ADJOURNMENT.

The *Annual General Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports from the Executive Secretary and Treasurer will be read; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. James Alex. Miller, will be inducted into office.

Thursday Evening, 8:00 o'Clock

Ballroom, Benjamin Franklin Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

The Toastmaster and the Guest Speakers will be announced in the Final Program.

FINAL GENERAL SESSION

Friday Afternoon, May 3, 1935

Presiding Officer

David P. Barr, St. Louis, Mo.

P.M.

2:00 A Study of the Comparative Vascular Disease in Patients with Obesity and Obese Patients with Diabetes.
Byron D. Bowen, Edgar Beck, James Fowler, and Edward Koenig, Buffalo, N. Y.
2:25 Arteriosclerosis and Hypertension in Diabetes.
Howard F. Root, Boston, Mass.
2:40 Does the High Carbohydrate-Low Calorie Diet Prevent Arteriosclerosis in Diabetics?
I. M. Rabinowitch, Montreal, Que.
3:05 Clinical Relationships of Blood Cholesterol with a Summary of our Present Knowledge of Cholesterol Metabolism.
Lewis M. Hurxthal, Boston, Mass.

3:30 INTERMISSION.

3:50 The Conservative Treatment of Gangrene and Infections in the Lower Extremities of Diabetics.
E. H. Mason, Montreal, Que.

4:10 Treatment of Peripheral Vascular Diseases by Means of Suction and Pressure.
Eugene M. Landis and Lewis H. Hitzrot, Philadelphia, Pa.

4:30 Recent Advances in Carbohydrate Metabolism, with Particular Reference to Diabetes Mellitus.
C. N. H. Long, Philadelphia, Pa.

4:50 The Treatment of Syphilis Complicating Tuberculosis.
C. Walter Clarke, New York, N. Y.

5:15 ADJOURNMENT.

PROGRAM OF MORNING LECTURES

With Lantern Slide and Moving Picture Demonstrations

This course of morning lectures is a new feature on the program of the Clinical Sessions of the College. The course is presented as an elective, as a whole or for individual days, in place of the hospital clinics. These lectures will be presented daily, Tuesday to Friday, inclusive, from 9:30 to 11:30, in the lecture room on the Exhibit floor of the Municipal Auditorium, 34th Street below Spruce Street.

The Morning Lectures will be devoted to four general topics: Diseases of the Bones and Joints, Neurology, Bronchopulmonary Diseases and Endocrinology. The speakers will present their subjects with the aid of lantern slides, moving pictures and other demonstrations.

The lectures will be open to all members of the College, guests of the College, members of the College of Physicians of Philadelphia, members of the Philadelphia County Medical Society and senior students of the various medical schools of Philadelphia. Due to limited capacity, *special tickets*, similar to the clinic tickets, *must be procured at the Registration Desk.*

Tuesday Morning, April 30, 1935

MUNICIPAL AUDITORIUM

(S. 34th St., below Spruce)

Lecture Room

Symposium on Diseases of the Bones and Joints

9:30–10:00 Roentgen Aspects of Bone Lesions.
Henry K. Pancoast and Philip J. Hodes, Philadelphia, Pa.

10:00–10:45 The Rôle of the Parathyroids in Diseases of the Bone.
Fuller Albright, Boston, Mass.

10:45–11:30 Arthritis: Etiologic Factors, Types and Treatment.
Ralph Pemberton, Philadelphia, Pa.

Wednesday Morning, May 1, 1935

MUNICIPAL AUDITORIUM
(S. 34th St., below Spruce)

Lecture Room

Symposium on Neurology

9:30–10:00 Neurosurgical Measures for Relief of Pain.
Francis C. Grant, Philadelphia, Pa.

10:00–10:30 Post-Encephalitic Behavior Problems in Childhood.
Earl D. Bond and Lauren H. Smith, Philadelphia, Pa.

10:30–11:00 Incipient Parkinsonism: A Diagnostic Triad for its Early Recognition.
A. M. Ornsteen, Philadelphia, Pa.

11:00–11:30 Regulation of Water Balance in the Symptomatic Treatment of Cerebral Disorders.
Temple Fay, Philadelphia, Pa.

Thursday Morning, May 2, 1935

MUNICIPAL AUDITORIUM
(S. 34th St., below Spruce)

Lecture Room

Symposium on Newer Methods of Treatment of Pulmonary and Bronchial Disease

9:30–10:00 Indications, Technique and Results of Collapse Therapy in Pulmonary Tuberculosis.
David A. Cooper, Philadelphia, Pa.

10:00–10:30 Oxygen Therapy in Pneumonia. (Demonstration, Discussion of Indications and Results.)
Leon H. Collins, Jr., Philadelphia, Pa.

10:30–11:00 The Bronchoscopic Treatment of Pulmonary Suppuration.
Louis H. Clerf, Philadelphia, Pa.

11:00–11:30 Recent Advances in Thoracic Surgery.
Richard H. Meade, Philadelphia, Pa.

Friday Morning, May 3, 1935

MUNICIPAL AUDITORIUM
(S. 34th St., below Spruce)

Lecture Room

Symposium on Endocrinology

9:30–10:00 Interrelationships of the Endocrine Glands.
Gerald T. Evans, Philadelphia, Pa.

10:00–10:30 A Lantern Slide Presentation of Endocrine Disorders.
Hans Lisser, San Francisco, Calif.

10:30–11:00 The Recognition and Treatment of Spontaneous Hyperinsulinism.
Seale Harris, Birmingham, Ala.

11:00–11:30 Classification and Treatment of Dwarfism.
James E. Cottrell, Philadelphia, Pa.

THE CLINIC SESSIONS

The program of the Clinic Sessions—Tuesday to Friday inclusive, from 9:00 A.M. to Noon—has been modelled on those which have proved so successful in recent years. Emphasis has been placed on clinics in the true sense of that word and there is scarcely a field of medicine which is not fully represented on the program. In addition to the various aspects of internal medicine, there are ample offerings in the subjects of pediatrics, psychiatry, neurology, roentgenology as well as in certain more distant fields which are still of importance to the internist, as for example bronchoscopy and certain surgical subjects. Ample opportunities in ward walks are offered for those who wish to see patients at close range and hospital methods in Philadelphia. Scientific demonstrations are offered on some programs that the visitors may see the research work actually being carried on at this time in the various laboratories.

The clinic program offers daily a capacity of over 3,000, scattered over eleven hospitals as well as some of the medical schools of the city. These hospitals are the following:

A The Children's Hospital, founded in 1855, the first in America and the second in the world to be devoted solely to children. Since 1930, a unit of the Department of Pediatrics of the School of Medicine of the University of Pennsylvania. It has 130 beds.

B The Graduate Hospital of the University of Pennsylvania, opened in 1928, functions as the teaching center for the Graduate School of Medicine of the University of Pennsylvania. It has a capacity of 500 beds and a large Outpatient Department.

C Temple University Hospital with 469 beds is the teaching hospital of the Medical Department of Temple University. This Hospital, the former Samaritan Hospital, was reorganized in 1891, renamed in 1929, and enlarged in 1932. It lies directly opposite the new Medical School Building, constructed in 1930.

D The Hospital of the University of Pennsylvania, established 61 years ago, was the first in this country to be identified with a university medical school. It has a capacity of 595 beds, a number of incorporated research departments and lies close to the Medical School Building.

E The Lankenau Hospital, originally the German Hospital, founded in 1860, has a capacity of 268 beds. The Research Institute of the Hospital is especially equipped for the study of cell growth as related to cancer. The Hospital is affiliated with the Graduate School of Medicine of the University of Pennsylvania.

F The Hahnemann Hospital is the teaching hospital of the Hahnemann Medical College, incorporated in 1848. A new hospital building was opened in 1928. The Hospital has a capacity of 700 beds.

G The Philadelphia General Hospital, the city hospital for treatment of those with diseases other than contagious ones. Developed from the hospital de-

partment of the original Alms House, founded 1732. For many years better known as "Blockley." Always a rich store house of clinical material for teaching purposes. Bed capacity, 2,500.

H The Presbyterian Hospital has grown steadily since its incorporation in 1871, new buildings being added in 1924, 1926, 1928 and 1931. It is an excellently equipped modern hospital. In 1933, there were 5,058 patients admitted, and 63,267 visits were made to the Outpatient Department.

J The Institute of the Pennsylvania Hospital is a division of the Pennsylvania Hospital. It was founded in 1929 for treatment and research in the psychoneuroses. It is affiliated with the Medical School of the University of Pennsylvania. It occupies a modern plant at 49th and Market Streets.

K The Hospital of the Jefferson Medical College was opened in 1877. It has 688 beds and a nine story modern Outpatient Department opened in 1931. It supplies ample facilities for teaching. There have been in the past year 12,737 admissions to the Hospital and 217,976 visits to the Outpatient Department.

L The Pennsylvania Hospital, founded in 1751, through the initiative of Benjamin Franklin, has been one of the leading hospitals of the city throughout its 184 years of service. Both Jefferson Medical College and the University of Pennsylvania make use of its facilities for teaching. Last year 6,459 patients were admitted and there were 154,566 visits to the Outpatient Department. Some of the original buildings are incorporated in the thoroughly modern plant.

Tickets will be required for each and every one of the special clinics, ward rounds and demonstrations unless specifically otherwise mentioned. The co-operation of everyone in securing his clinic tickets will assist greatly in distributing the attendance according to the capacity of each program. It is self-evident that a ward round arranged for fifteen will lose its value for all if forty or fifty are present. Ticket registration naturally is the only effective method of keeping the attendance within the capacities indicated.

To all members of the College, registration blanks for the clinics and demonstrations will be distributed with the formal program. Upon receipt of application for clinic reservations by the Executive Secretary, *proper tickets will be selected and held at the Registration Bureau at Philadelphia.* Reservations by mail cannot be made after April 20, but reservations may be made in person at the Registration Bureau on the evening preceding any clinic day. *Guests will kindly register for clinics at the Registration Bureau upon arrival at Philadelphia.*

PROGRAM OF CLINICS

Tuesday, April 30, 1935

A 1 — CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Catherwood House
(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

9:00–10:00 Chorea.
John P. Scott.

10:00–10:30 Stovarsol in Treatment of Prenatal Syphilis.
Donald M. Pillsbury and H. H. Perlman.

10:30–11:00 Differentiation between Meningism and Meningitis.
Charles F. McKhann, Boston, Mass.

11:00–11:30 Diagnosis and Treatment of Pollen Asthma in Children, with Demonstration.
S. C. Copeland.

11:30–12:00 Continuous Venoclysis in Intestinal Intoxication of Infants, with Use of Glucose, Salts, Serum and Fat.
Mitchell I. Rubin and Horace L. Hodes.

A 2 — CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)
(Entrance, Bainbridge Street below 18th)

Ward Walk

(Capacity, 10)

9:00–10:20 Ward Walk.
Joseph Stokes, Jr.

A 3 — CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease
(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

10:30–11:00 Demonstration of Influence of Diet upon Natural Resistance to Infection of Mice.
Charles F. Church.

11:00–11:30 Demonstration of Adrenalectomy in Rats: Results of Treatment with Salts.
Elizabeth Krick.

11:30–12:00 Treatment in Convulsant Poisons.
Joseph Stokes, Jr.

Tuesday, April 30, 1935 (Continued)

B 1 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

9:00– 9:30 Relief of Pericardial Constriction by Surgical Means: Case Presentations.
W. Estell Lee and George C. Griffith.

9:30–10:00 Coronary Artery Disease.
George Morris Piersol.

10:00–10:30 Cure of Angina Pectoris by Section of the Posterior Thoracic Nerve Roots.
Francis C. Grant and George C. Griffith.

10:30–11:20 Use of Digitalis and its Glucosides.
William D. Stroud.

11:20–12:00 The Lymphoblastomas.
Edward Steinfield.

B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

9:00– 9:20 Demonstration of the Anatomical Significance of the Cryptal Epithelium in Tonsillar Infections.
George B. Wood.

9:20– 9:40 Bronchosinusitis in Childhood.
Howard Childs Carpenter.

9:40–10:10 Factors Leading to Selective Collapse of the Lung Following Pneumothorax.
Richard T. Ellison.

10:10–11:00 Squint—Practical Demonstration for Orthoptic Training.
Luther Peter.

11:00–12:00 Selected Dermatologic Cases.
Robert L. Gilman and Sigmund S. Greenbaum.

B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Assemble at Private Admissions' Desk

Demonstrations and Ward Clinics

(Capacity, 15)

9:00–10:00 Lymphopathia Venerium—Proctologic Clinic.
Collier Martin and Staff.

Tuesday, April 30, 1935 (Continued)

10:00–12:00 Gastro-enterological Clinic:
(a) Sigmoidoscopic and Roentgenographic Demonstration of Cases of Ulcerative Colitis.
(b) Demonstration of Takata and other Liver Function Tests.
(c) Bile Microscopy in the Diagnosis of Gall Tract Disease.
H. L. Bockus, Henry Tumen, Harry Metzger and Staff.

C 1 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Auditorium, 3d Floor, Medical Building

(Capacity, 250)

9:00– 9:30 Alternating Negative and Positive Pressures in the Treatment of Vascular Diseases.
Frank H. Krusen.

9:30–10.00 Determination of Heart Size by Roentgenologic Methods.
Hugo Roesler.

10:00–10:30 The Nine Lead Electrocardiogram; Its Value in Angina Pectoris: Preliminary Report.
Joseph B. Wolffe.

10:30–11:00 Fundal Changes in the Hypertensive Diseases.
Walter I. Lillie.

11:00–12:00 The Differentiation of Circulatory Failure of Peripheral and Cardiac Origin.
Arthur M. Fishberg, New York, N. Y.

C 2 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Surgical Amphitheatre, 3d Floor, Hospital

(Capacity, 100)

9:00– 9:30 The Use of Iron and Arsenic in Secondary Anemias in Children.
Ralph M. Tyson.

9:30–10.00 Newer Aspects of Pediatric Therapy.
H. H. Perlman.

10:00–10:30 The Relation between Psychoneurosis and Anorexia in the Young Child. (Motion Picture Demonstration.)
Gerald H. J. Pearson.

10:30–11:00 Similarity of Throat Appearance in Diphtheria and Agranulocytosis.
Pascal F. Lucchesi.

11:00–12:00 Discussion of Fluid Restriction Regime and Its Application to Pediatric Problems.
Temple Fay.

Tuesday, April 30, 1935 (Continued)

C 3 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Medical School Building, Room 603

(Capacity, 100)

9:00– 9:30 The Influence of Various Drugs on Allergic Reactions.
Louis Tuft and M. L. Brodsky.

9:30–10:00 An Intradermal Test for Malignancy.
Benjamin Gruskin.

10:00–10:30 Vaccination against Pneumococcus Infection with Special Reference to Pneumonia.
John A. Kolmer.

10:30–11:00 An Objective Method to Demonstrate Hyperalgesic Zones in Visceral Diseases.
Ernst Spiegel and Michael G. Wohl.

C 4 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

X-Ray Museum, 6th Floor, Medical School Building

(Capacity, 50)

9:00–10:30 Chest Conference: Bronchial Carcinoma; Bronchiectasis and Pulmonary Suppuration; Tuberculosis.

Roentgenology
W. Edward Chamberlain.

Bronchoscopy
C. L. Jackson.

Clinical Aspects
Edward Weiss.

Chest Surgery
W. Emory Burnett.

Tuberculosis
Louis Cohen.

Pathology
Frank W. Konzelmann.

10:30–11:00 Chronic Adhesive Pericarditis.
Hugo Roesler.

C 5 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Outpatient Department, 2d Floor, Medical School Building

(Capacity, 20)

11:00–12:00 Demonstration of the Retinal Changes in Medical and Neurological Conditions by Means of the Multiocular Ophthalmoscope.
Walter I. Lillie and Glen G. Gibson.

Tuesday, April 30, 1935 (Continued)

C 6 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Ward 3 C, Hospital

(Capacity, 15)

11:00–12:00 Ward Walk.
Roy L. Langdon.

C 7 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

(Unlimited—No Tickets Required)

11:00–12:00 Demonstrations and Exhibits in Various Departments of the Hospital and Medical School—Special Hospital Program will be available.

D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Medical Clinic

(Capacity, 175)

9:00– 9:45 Medical Diagnostic Clinic.
O. H. Perry Pepper.

9:45–10:15 Clinic on Diabetes with Special Reference to the Course of the Disease as Influenced by Treatment.
Russell Richardson.

10:15–10:45 Some Considerations Dealing with Pyrexia.
J. Harold Austin.

10:45–11:00 Clinical Vitamin B Deficiency.
Katherine O'S. Elsom.

11:00–12:00 X-Ray Conference.
Henry K. Pancoast and Ward Physicians on Service.

D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Bronchoscopic Clinic

(Capacity, 100)

9:00– 9:30 Clinic on Renal Function.
Eugene M. Landis.

9:30–10:00 Recent Advances in the Knowledge of Heart Sounds.
Alexander Margolies.

10:00–10:30 Glycosuria—Diabetic and Non-Diabetic: Case Presentations.
Leon Jonas.

10:30–10:45 Follow-up Study of Patients Diagnosed as Neuroses.
Bernard I. Comroe.

Tuesday, April 30, 1935 (Continued)

10:45–11:00 Peripheral Type of Facial Palsy in Vascular Conditions: Case Presentation.
J. Q. Griffith, Jr.

11:00–12:00 Pulmonary Complications following Surgical Operations.
Gabriel Tucker.

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a

9:00–10:30 Ward B.
Lewis H. Hitzrot.

D 3b

9:00–10:30 Ward D.
T. Grier Miller.

D 3c

9:00–10:30 Pepper Ward.
Francis C. Wood.

Three above groups will alternate for the three following sets of demonstrations.

Demonstrations in Maloney Clinic

10:30–11:00 8th Floor.
Relation between Adrenals, Pituitary Body and Diabetes Mellitus.
C. N. H. Long and Staff.
6th Floor, Department of Biophysics.
Use of Short Wave Diathermy in Internal Medicine.
D. W. Bronk and J. P. Herbey.

3d Floor, Gastro-intestinal Department.
Clinical Studies of Small Intestine.
T. Grier Miller and Staff.

11:00–11:30 Room 218.
Immunity in Diabetes.
Russell Richardson.
Room 709.
Complement Fixation in Amoebiasis: Nature of Test; Value in Acute and Chronic States; Value of Cultural, Wet Smear and Complement Fixation Methods.
James S. Forrester.
Room 709.
New Method for Discovery of Sickle Cells in the Blood: Method to Discover the Trait that Develops Sickle Cells; Method for Permanent Films; Some Clinical Data.
James S. P. Beck.

Tuesday, April 30, 1935 (Continued)

Room 701.
Colorimetric Readings by the Method of Optical Filters (Photronic Cells): Determination of Hemoglobin, Blood Sugar, Phosphates, etc.; New Procedure for the Measurement of Serum Volume.
F. William Sunderman.

11:30–12:15 Room 311, Robinette Foundation.
Demonstration of the Use of Chest Leads in Electrocardiography. This demonstration will be of interest only to those with some knowledge of Clinical Electrocardiography.
Room 801.
Determination of pH in Blood and Serum by the Glass Electrode.
W. C. Stadie.
5th Floor.
Inspection of Department of Physiotherapy. Discussion of various procedures.
Josef B. Nylin.

D 4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL BUILDING

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

9:00– 9:15 Pituitary and Experimental Hypothyroidism.
Isolde T. Zeckwer.

9:15– 9:30 Experimental Anemia of Renal Insufficiency.
Neil McLeod.

9:30– 9:55 Experiments on Chemotropism of Human Leukocytes and Lymphocytes.
Morton McCutcheon and H. M. Dixon.

9:55–10:20 Adenocarcinoma in Frogs Possibly Associated with a Filterable Virus.
Balduin Lucké.

10:20–10:30 Iron Balance in Experimental Anemia in Dogs.
Elizabeth D. Wilson.

10:30–12:00 Demonstrations in Department of Pathology: Room 264.
(1) Demonstrations of above Papers.
The Staff.
(2) Gross Specimens.
Dale R. Coman et al.
(3) Demonstration of Gross and Miscroscopic Specimens illustrating various Forms of Bone Disease.
George Wagoner.
Demonstrations from Department of Research Dermatology.
(1) Torulosis.
(2) Xanthomatosis.
Fred D. Weidman.

There will also be demonstrations open to inspection from 9:00 to 12:00 in the Departments of Bacteriology and Research Surgery.

Tuesday, April 30, 1935 (Continued)

E 1 LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

Amphitheatre

(Capacity, 100)

9:00– 9:30 Leukemia.
Frederick L. Hartmann.

9:30–10:00 Status Thymicolymphaticus.
Edward H. Campbell.

10:00–10:30 Clinic on Diseases of the Skin.
John B. Ludy.

10:30–11:00 Treatment of Epithelioma.
Robert Shoemaker, 3d.

11:00–12:00 Oxygen Therapy in Pneumonia, Cardiac and Cardiorespiratory Disturbances.
Alvan Barach, New York, N. Y.

E 2 LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

Nurses' Lecture Hall

(Capacity, 50)

9:00– 9:30 Human Infertility: Modern Treatment.
Bradford Green.

9:30–10:00 Dysmenorrhea: Discussion of Hormone Therapy.
Ross B. Wilson.

10:00–10:30 Non-allergic Vasomotor Rhinitis and Underlying Emotional Factors.
Ralph Butler and Clarence A. Patten.

10:30–11:00 Emotional Factors and the Allergic State.
Harry B. Wilmer.

11:00–11:30 Obesity in Children: Treatment.
Julian M. Lyon.

11:30–12:00 Obesity in Adults: Dinitrophenol.
Edward L. Bortz.

E 3 LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

Men's Medical Ward, Second Floor

(Capacity, 15)

11:00–12:00 Ward Rounds.
Frederick L. Hartmann.

F HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Elkins Amphitheatre, 3d Floor

(Capacity, 200)

9:00– 9:45 Dermatological Clinic.
Ralph Bernstein and Paul Wittman.

Tuesday, April 30, 1935 (Continued)

9:45–10:30 Diagnosis and Treatment of Thyroid Deficiency.
Lewis M. Hurxthal, Boston, Mass.

10:30–11:00 Pituitary Dysfunction with Infantile Gonadism.
Donald R. Ferguson.

11:00–12:00 Clinicopathological Conference.
Samuel W. Sappington.

G 1 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Auditorium

(Capacity, 200)

9:00– 9:35 Superior Sulcus Tumors.
Henry K. Pancoast.

9:35–10:20 Pulmonary Carcinoma.
Herbert Lund, Bernard Widmann and Herman W. Ostrum.

10:20–10:40 Orthostatic Hypotension.
Truman G. Schnabel.

10:40–11:05 High Blood Urea Nitrogen not due to Chronic Glomerulonephritis.
Raymond Brust.

11:05–11:20 Roentgenological Studies:
(1) The Bones in Diseases of the Ductless Glands.
(2) Pulmonary Lesions Simulating Tuberculosis.
Herman W. Ostrum.

11:20–11:30 The Accuracy of Clinical Diagnoses Based on 1100 Consecutive Postmortems.
Jefferson H. Clark.

11:30–12:00 Obesity with Especial Reference to Salt Water Retention.
Michael G. Wohl.

G 2 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Clinical Amphitheatre

(Capacity, 250)

9:00– 9:30 Studies of the Myopathies from a Chemical Pathological and Experimental Standpoint.
John G. Reinhold, Mr. George Kingsly and R. P. Custer.

9:30–10:30 Muscular Affections.
J. W. McConnell.
Walter M. Boothby, Rochester, Minn.

10:30–10:40 Non-stenosing Esophageal Carcinoma.
R. W. Mathews.

10:40–11:30 The Reticuloendothelial System and its Relation to Disease.
R. P. Custer.

11:30–12:00 Mercury Intoxication Treated by Sodium Formaldehyde Sulphoxylate.
William Egbert Robertson.

Tuesday, April 30, 1935 (Continued)

G 3 PHILADELPHIA GENERAL HOSPITAL

(34th Street below Pine)

Medical Section Building

(Capacity, 15)

9:00–10:00 Ward Walk.
Howard W. Schaffer.

H 1 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

9:00– 9:50 Changing Views on Arterial Hypertension.
Joseph Barach, Pittsburgh, Pa.

9:50–10:35 Pneumothorax in Lobar Pneumonia.
Thomas Klein.

10:35–11:15 Neurological Clinic: Parkinsonian Syndrome in Chronic Epidemic Encephalitis.
Williams B. Cadwalader and Samuel Hadden.

11:15–12:00 Sickle Cell Anemia.
Truman G. Schnabel.

H 2 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Ladies Aid Room

(Capacity, 65)

9:00– 9:30 Quantitative Methods of Testing Deafness.
Douglas Macfarlan.

9:30–10:00 Yeast Infections of the Mouth and Throat.
Douglas Macfarlan.

10:00–10:30 Neutrophilic Response to Infections of the Upper Respiratory Tract.
Walter Cariss.

10:30–12:00 Clinical-Pathological Conference:
Aortic Aneurysms.
George C. Griffith, Mary Easby and Kenneth E. Fowler.
Femoral Aneurysms.
Ernest Williamson and Kenneth E. Fowler.

H 3 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Medical Ward

(Capacity, 15)

9:30–10:30 Ward Rounds.
J. T. Beardwood, Jr., and Herbert T. Kelly.

At 10:30 those making ward rounds may join the Clinical-Pathological Conference in the Ladies Aid Room.

Tuesday, April 30, 1935 (Continued)

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL
(111 North 49th Street)

No Program on Tuesday

K 1 JEFFERSON HOSPITAL
(10th and Sansom Streets)

Clinical Amphitheatre
(1020 Sansom Street)

(Capacity, 250)

9:00– 9:30 Purpura Hemorrhagica: Experimental and Pathological.
Leandro Tocantins.

9:30–10:00 Purpura Hemorrhagica: Surgical and Medical Treatment.
Harold W. Jones.

10:00–11:00 (1) Control of the Growth of Bones in the Lower Extremities.
(2) Mechanical Factors in Low Back Pain.
(3) Treatment of Poliomyelitis.
J. Torrance Rugh.

11:00–11:30 Diagnostic Significance of Shoulder Top Pain.
Fred J. Kalteyer.

11:30–12:00 Familial Rheumatic Fever.
Edward J. G. Beardsley.

K 2 JEFFERSON HOSPITAL
(10th and Sansom Streets)

Second Floor Medical

(Capacity, 15)

11:00–12:00 Ward Walk.
Martin E. Rehfuss.

L 1 PENNSYLVANIA HOSPITAL
(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Hospital Chapel

(Capacity, 200)

George W. Norris presiding

9:00–10:00 The Rôle of the X-Ray in the Diagnosis and Supervision of Tuberculosis.
F. Maurice McPhedran, Henry Phipps Institute, University of Pennsylvania.

10:00–11:00 Clinic on Pulmonary Tuberculosis.
James Alex. Miller, New York, N. Y.

11:00–11:30 The Physiological Disturbances Produced by an Arteriovenous Aneurysm.
Louis B. Laplace.

Tuesday, April 30, 1935 (Continued)

11:30–12:00 Matas Obliterative Aneurysmorrhaphy. (Motion Picture.)
W. Estell Lee.

9:00–1:00 P.M. The Library of the Pennsylvania Hospital, which is the first Medical Library of this country, will be open from 9:00 until 1:00 daily. Dr. Francis R. Packard is in charge of arranging this exhibit.

L 2 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Surgical Clinic

(Capacity, 200)

David L. Farley presiding

9:00– 9:30 Analysis of Cases of Pellagra Admitted to the Pennsylvania Hospital during the Past Ten Years.
Thomas C. Garrett.

9:30–10:00 Lymphogranuloma Inguinale and its Relation to Rectal Stricture.
Joseph V. Vander Veer.

10:00–11:00 Medical Clinic.
James H. Means, Boston, Mass.

11:00–11:30 Cirrhosis of the Liver.
W. Grady Mitchell.

11:30–12:00 Fever of Obscure Origin.
David L. Farley.

L 3 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Ward Rounds

1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

9:00–10:00 Wards 3 and 4.
David L. Farley and Associates.

L 3b

9:00–10:00 Wards 1 and 4.
Thomas McCrae, Robert P. Regester and Associates.

Two above groups will consolidate for balance of program.

Ayer Clinical Laboratory

(Capacity, 24)

10:00–11:00 Clinicopathological Conference.
John T. Bauer.
Discussion, opened by Esmond R. Long.

Tuesday, April 30, 1935 (Continued)

Outpatient Department

11:00–11:30 Children's Heart Clinic Demonstration.
Thomas M. McMillan.

11:30–12:00 The Administration of a Hospital Outpatient Department.
Samuel Bradbury.

Wednesday, May 1, 1935

A 1 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Catherwood House
(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

9:00–10:00 The Antirachitic Effect of Evaporated and Liquid Irradiated Milk: A Controlled Study.
Joseph Stokes, Jr.

10:00–10:30 The Results of the Use of Ascorbic Acid.
Milton Rapoport.

10:30–11:00 The Use of Molar Sodium Lactate in Diabetic Coma.
Horace L. Hodes.

11:00–12:00 The Modern Treatment of Squint.
A. G. Fewell.

A 2 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)
(Entrance, Bainbridge Street below 18th)

Ward Walk

(Capacity, 10)

9:00–10:20 Ward Walk.
Mitchell I. Rubin.

A 3 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease
(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

10:30–11:00 Lyophile Serum.
Aims C. McGuinness.

11:00–11:30 Demonstration of Rats Exhibiting Fat Deficiency Syndrome.
Dorothy V. Whipple.

11:30–12:00 Essential Hypertension in Children, with Demonstration of Pathological Specimens.
James J. Reilly and Irving J. Wolman.

Wednesday, May 1, 1935 (Continued)

B 1 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

9:00– 9:40 Diagnosis and Treatment of Cancer of Bladder.
George Pfahler.

9:40–10:20 Posture in Relation to Diagnosis: Case Presentations.
William Bates and John Howell.

10:20–11:00 The Relation of Calcium-Phosphorus Metabolism to Certain Bone Diseases.
(*a*) Theoretical and Experimental Aspect.
George Wagoner.
(*b*) Clinical Aspect.
DeForest P. Willard.

11:00–12:00 Pulmonary Emphysema.
Henry M. Thomas, Jr., Baltimore, Md.

B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

9:00– 9:40 Determination of the Phagocytic Power of Whole Blood or Plasma-leukocyte Mixtures for Clinical or Experimental Purposes.
Fred Boerner and Stuart Mudd.

9:40–10:30 Rectal Stricture due to Lympopathia Venerium.
Collier Martin.

10:30–11:00 Advisability of Medical Examination Preliminary to Gynecologic Operation.
William R. Nicholson and Henry Tumen.

11:00–12:00 Diagnosis and Treatment of Functional Menstrual Disorders: Demonstration of Patients.
Charles Mazer.

B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Assemble at Private Admissions' Desk

Demonstrations and Ward Clinics

(Capacity, 15)

9:00–10:00 Gastroscopic Clinic.
Gabriel Tucker.

10:00–11:00 Roentgenologic Consideration of Interesting Gastro-intestinal Cases.
Karl Kornblum.

Wednesday, May 1, 1935 (Continued)

11:00–12:00 Ward Clinic. Neurological Cases.
Clarence A. Patten.

C 1 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Auditorium, 3d Floor, Medical Building

(Capacity, 250)

9:00– 9:45 Vaccination against Acute Poliomyelitis.
John A. Kolmer.

9:45–10:15 Recent Progress in the Prevention and Treatment of Eclampsia.
Jesse O. Arnold.

10:15–11:00 Clinicopathologic Conference: The Evolution of Chronic Glomerulonephritis Including a Discussion of the Fundal Changes.
Edward Weiss, Frank W. Konzelmann, Walter I. Lillie and Glen G. Gibson.

11:00–12:00 Nephrosis.
William S. McCann, Rochester, N. Y.

C 2 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Surgical Amphitheatre, 3d Floor, Hospital

(Capacity, 100)

9:00– 9:30 Bronchial Carcinoma: Bronchoscopic Biopsy.
C. L. Jackson and Frank W. Konzelmann.

9:30–10:00 Hoarseness: Laryngofissure for Early Carcinoma of the Larynx.
Chevalier Jackson.

10:00–10:30 Laryngectomy for Carcinoma of the Larynx.
W. Wayne Babcock.

10:30–11:00 The Behavior of Cavities in Pulmonary Tuberculosis.
A. J. Cohen.

C 3 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Medical School Building, Room 603

(Capacity, 100)

9:00– 9:30 Vertigo with Special Reference to Cortical Localization of the Labyrinth.
Ernst Spiegel.

9:30–10:15 The Mechanism of Headache: Its Analysis and Treatment.
Temple Fay.

10:15–11:00 The Hydrostatics and Hydrodynamics of the Cerebrospinal Fluid System with Special Reference to Encephalography.
W. Edward Chamberlain and Nicholas Gotten.

Wednesday, May 1, 1935 (Continued)

11:00–11:30 The Diagnosis of Tumors of the Brain.
Nathaniel W. Winkelman.

11:30–12:00 The Diagnosis of Intracranial Lesions from the Ophthalmological Standpoint.
Walter I. Lillie.

C 4 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Department of Bronchoscopy, Hospital

(Capacity, 20)

11:00–12:00 Demonstration: Technique of the Instillation of Lipiodol for Bronchography.
C. L. Jackson.

C 5 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Outpatient Department, 1st Floor, Medical School Building

(Capacity, 20)

11:00–12:00 Biliary Drainage with Special Reference to Cytology and Parasitic Infestation (Demonstration.)
Charles-Francis Long and W. A. Swalm.

C 6 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Ward 2 C, Hospital

(Capacity, 15)

11:00–12:00 Ward Walk.
Allen G. Beckley.

C 7 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

(Unlimited—No Tickets Required)

11:00–12:00 Demonstrations and Exhibits in Various Departments of the Hospital and Medical School—Special Hospital Program will be available.

Wednesday, May 1, 1935 (Continued)

D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Medical Clinic

(Capacity, 175)

9:00- 9:45 Clinic on Pulmonary Actinomycosis.
Sydney R. Miller, Baltimore, Md.

9:45–10:15 Dwarfism: Observations on Treatment. Illustrative Cases.
James E. Cottrell.

10:15–10:45 Discussion of Possibility and Value of Desensitization in the Treatment of Arthritis.
Herbert Fox.

10:45–11:30 Heart Disease in Relation to Surgery.
Alfred Stengel.

11:30–12:00 Clinicopathological Conference.
Balduin Lucké and Medical Staff.

D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bronchoscopic Clinic

(Capacity, 100)

9:00– 9:30 Clinic on Coronary Occlusion.
Francis C. Wood.

9:30–10:00 Oxygen Administration in Pneumonia.
Leon H. Collins, Jr.

10:00–10:15 Amyloid Nephrosis.
F. William Sunderman.

10:15–10:30 Irradiation Reactions in the Lungs.
J. R. Andrews.

10:30–10:45 Renal Changes in Hyperparathyroidism.
Kendall Elsom.

10:45–11:00 Spinal Cord Involvement in Hodgkin's Disease.
Melbourne J. Cooper.

11:00–11:15 Extrinsic Factors Influencing the Sedimentation Rate.
Harry Flippin.

11:15–11:30 Influence of Chest Deformities on the Heart and Great Vessels.
Joseph Edeiken.

11:30–12:00 Certain Types of Cardiac Involvement Encountered in Coroner's Examinations; Observations on their Clinical Significance.
Martin P. Crane.

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a
9:00–10:30 Ward B.
Thomas Fitz-Hugh, Jr.

Wednesday, May 1, 1935 (Continued)

D 3b

9:00–10:30 Ward D.
Simon S. Leopold.

D 3c

9:00–10:30 Pepper Ward.
Eugene M. Landis.

Three above groups will alternate for the three following sets of demonstrations.

Demonstrations in Maloney Clinic

10:30–11:00 8th Floor.
Relation between Adrenals, Pituitary Body and Diabetes Mellitus.
C. N. H. Long and Staff.
6th Floor, Department of Biophysics.
Use of Short Wave Diathermy in Internal Medicine.
D. W. Bronk and J. P. Herbey.
3d Floor, Gastro-intestinal Department.
Clinical Studies of Small Intestine.
T. Grier Miller and Staff.

11:00–11:30 Room 218.
Immunity in Diabetes.
Russell Richardson.
Room 709.
Complement Fixation in Amoebiasis: Nature of Test; Value in Acute and Chronic States; Value of Cultural, Wet Smear and Complement Fixation Methods.
James S. Forrester.
Room 709.
New Method for Discovery of Sickle Cells in the Blood: Method to Discover the Trait that Develops Sickle Cells; Method for Permanent Films; Some Clinical Data.
James S. P. Beck.
Room 701.
Colorimetric Readings by the Method of Optical Filters (Photronic Cells): Determination of Hemoglobin, Blood Sugar, Phosphates, etc.; New Procedure for the Measurement of Serum Volume.
F. William Sunderman.

11:30–12:15 Room 311, Robinette Foundation.
Demonstration of the Use of Chest Leads in Electrocardiography. This demonstration will be of interest only to those with some knowledge of Clinical Electrocardiography.
Room 801.
Determination of pH in Blood and Serum by the Glass Electrode.
W. C. Stadie.
5th Floor.
Inspection of Department of Physiotherapy. Discussion of various procedures.
Josef B. Nylin.

Wednesday, May 1, 1935 (Continued)

D 4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL BUILDING

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

9:00– 9:20 A Study of Cystinuria.
J. C. Andrews.

9:20– 9:40 Rickets and Parathyroid Glands.
J. H. Jones.

9:40–10:00 Movements of Mammalian Fetuses. (Motion Picture Demonstration.)
E. A. Swenson.

10:00–10:30 Motion Pictures of Circulation in the Rabbit's Ear.
E. R. Clark and E. A. Swenson.

10:30–12:00 Demonstrations in the Department of Anatomy:

(1) Microscopic Studies on Living Mammalian Blood Vessels and Other Tissues, in Transparent Chambers.
E. R. Clark, E. L. Clark and Associates.

(2) A Transparent Chamber Permitting Access for Cell Cultures, Transplantation, or Manipulations in the Living Mammal.
R. G. Williams.

(3) Models of the Basal Ganglia of the Human Brain.
W. H. F. Addison and Doris A. Fraser.

(4) Venous Circulation of the Skull, with Especial Reference to its Significance in Infections.
O. V. Batson.

(5) Microdissection of Living Cells.
G. S. deRenyi.

(6) Growth and Behavior of Living Nerve Cells in an Electric Field.
S. C. Williams.

(7) *a*—Changes in the Fish Retina after Cutting the Optic Nerve and Retinal Blood Vessels.
b—The Effects of Pituitary Extracts on Sexual Activity in a Species of Fish.
S. A. Matthews.

(8) The Behavior of Tissue Culture Cells in the Presence of Amoebicidal Drugs.
M. J. Hogue.

(9) A Case of Pseudohemaphroditism in a Hyena (Specimen from Philadelphia Zoological Garden).
C. D. Van Cleave.

(10) General and Local Structural Changes in the Intestine of the Rat when Fed Unbalanced, Artificial Diets.
J. L. Wierda.

There will also be demonstrations open to inspection from 9:00 to 12:00 in the Departments of Pathology, Bacteriology and Research Surgery.

Wednesday, May 1, 1935 (Continued)

E 1 LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

Amphitheatre

(Capacity, 100)

9:00–10:00 Diabetes.
I. M. Rabinowitch, Montreal, Que.

10:00–10:30 Juvenile Diabetes.
Walter M. Bortz, Greensburg, Pa.

10:30–11:00 Studies of the Peripheral Vascular System.
William B. Wartman.

11:00–11:30 Treatment of Surgical Lesions in Diabetes.
Damon B. Pfeiffer and J. Montgomery Deaver.

11:30–12:00 Chronic Middle Ear Infection: Diagnosis and Treatment.
James A. Babbitt.

E 2 LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

Research Institute

(Capacity, 50)

9:00– 9:30 Importance of Cystine in Growth and Development.
M. A. Bennett.

9:30–10:00 The Oxidation Products of Cystine.
Gerrit Toennies.

10:00–10:30 Chemical Relations of Cholesterol, Carcinogenic Substances and Certain Hormones.
Theodore F. Lavine.

10:30–11:00 Protection against Carcinogenesis afforded by Sulphydryl.
Stanley P. Reimann.

11:00–11:30 Presentation of Precision Methods for Determining Sulphur.
K. Shinohara.

11:30–12:00 Proteinuria.
Grace Medes.

E 3 LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

Men's Medical Ward, Second Floor

(Capacity, 15)

11:00–12:00 Ward Rounds.
Edward L. Bortz.

F HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Elkins Amphitheatre, 3d Floor

(Capacity, 200)

9:00– 9:30 Clinical Problems in Pneumonia.
E. Roland Snader, Jr.

9:30–10:15 Demonstration of the Taking of Intragastric Temperature Curves and Intragastric Photography.
Harry M. Eberhard.

Wednesday, May 1, 1935 (Continued)

10:15–10:45 Total Thyroidectomy in Intractable Heart Failure.
Milton J. Raisbeck, New York, N. Y.

10:45–11:15 Non-Colloidal Sulphur in the Treatment of Arthritis.
Lowell L. Lane and Peter J. Warter.

11:15–12:00 Clinical Roentgenological Conference on Tuberculosis.
George G. Ornstein, New York, N. Y.
Joseph W. Post.

G 1 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Auditorium

(Capacity, 200)

9:00– 9:30 Cerebral Histanoxia as a Complication of Severe Systemic Disorders.
Helena Riggs.

9:30–10:15 Cerebral Vascular Disease.
Clarence A. Patten.

10:15–11:00 Psychopathology in Internal Medicine.
Edward A. Strecker.

11:00–11:15 Transcerebral Diathermy in Parkinsonism.
Samuel Hadden and A. A. Martucci.

11:15–12:00 Changes in the Chemistry and Composition of the Blood in Mental States.
Seymour DeWitt Ludlum.

G 2 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Clinical Amphitheatre
(Capacity, 100)

8:00– 9:30 Aneurysm, Congestive Failure, Cardiac Pain and Peripheral Vascular Disease; their Surgical Aspects.
W. Wayne Babcock.

9:30–10:30 Somatic Symptoms as Part of an Early Schizophrenic Reaction.
O. Spurgeon English.

10:30–11:30 Endocrinopathies.
Samuel A. Loewenberg.

11:30–12:00 Oral Diseases with Special Reference to Syphilis.
Sigmund S. Greenbaum.

12:00–12:30 Multiple Neuritis.
George Wilson.

G 3 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Medical Section Building

(Capacity, 15)

10:00–12:00 Ward Walk.
Fred J. Kalteyer.

Wednesday, May 1, 1935 (Continued)

G 4 PHILADELPHIA GENERAL HOSPITAL

(34th Street below Pine)

Department of Metabolism

(Capacity, 25)

9:00–10:00 The Philadelphia General Hospital Method of Standardizing the Diabetic.
Reuben Davis.

10:00–11:00 (*a*) Treatment of Diabetic Coma.
(*b*) Cerebral Lesions Found in Six Uncomplicated Cases of Diabetic Coma.
W. Wallace Dyer.

11:00–12:00 (*a*) Results of Neglected Diabetes Mellitus.
Edward S. Dillon.
(*b*) Presentation of Interesting Cases of Diabetes Mellitus.
Lewis H. Hitzrot.

H 1 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

9:00– 9:50 Clinic on Hypertension.
Louis Warfield, Milwaukee, Wis.

9:50–10:20 Modified Tetralogy of Eisenmenger.
James E. Talley and Kenneth E. Fowler.

10:20–10:40 Cardiovascular Disease in Patients with Myomata.
Ferdinand Fetter.

10:40–11:20 Hyperthyroidism in Pregnancy.
Collin Foulkrod and Frederick A. Bothe.

11:20–12:00 Electrocardiographic Studies in Pericardial Disease.
George C. Griffith.

H 2 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Ladies' Aid Room

(Capacity, 65)

9:00– 9:30 Value and Limitation of Tests for Pancreatic Function.
Thomas Johnson.

9:30–10:10 Glucose Tolerance Tests: Methods, Value and Danger.
Herbert T. Kelly.

10:10–10:30 Glucose Tolerance Tests in Epilepsy.
Joseph R. Pierson.

10:30–12:00 Clinical-Pathological Conference:
Endocarditis, Subacute, Bacterial.
Truman G. Schnabel and Kenneth E. Fowler.
Ruptured Heart.
Thomas Klein and Kenneth E. Fowler.

Wednesday, May 1, 1935 (Continued)

H 3 PRESBYTERIAN HOSPITAL
(39th Street and Powelton Avenue)

Medical Ward

(Capacity, 15)

9:30–10:30 Ward Rounds.
Thomas Klein.

At 10:30 those making ward rounds may join the Clinical-Pathological Conference in the Ladies' Aid Room.

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL
(111 North 49th Street)

Auditorium

(Capacity, 250)

9:00– 9:20 Introduction.
Edward A. Strecker.

9:20– 9:40 Medical Aspect of the Neuroses.
Lauren H. Smith.

9:40–10:00 Psychoanalytic-Medical Relationships.
Kenneth E. Appel.

10:00–10:20 Physiologic Factors in Psychiatric Research.
Harold D. Palmer.

10:20–10:40 The Response of the Spinal Cord to Two Stimuli.
Joseph Hughes.

10:40–11:00 Post-Encephalitic Behavior Disorders.
Earl D. Bond.

11:00–12:00 Historical Exhibit (Library of the Parent's Council). Books and Curiosa Relating to Psychiatry.
Clifford B. Farr.

Inspection of the Institute, Laboratories and Franklin School.

K 1 JEFFERSON HOSPITAL
(10th and Sansom Streets)

Clinical Amphitheatre
(1020 Sansom Street)

(Capacity, 250)

9:00– 9:20 The Determination of the Liver Function in Diseases of the Biliary Tract.
A. Cantarow.

9:20– 9:40 Differential Diagnosis of Diseases of the Liver.
B. B. Vincent Lyon.

9:40–10:00 Surgical Aspect of Diseases of the Liver.
Charles F. Nassau.

10:00–11:00 Clinicopathological Conference.
Edward J. G. Beardsley, Baxter L. Crawford and Kenneth E. Fry.

Wednesday, May 1, 1935 (Continued)

11:00–12:00 The Diagnosis and Treatment of Bronchiectasis.
Roentgen Ray.
John T. Farrell, Jr.
Bronchoscopic.
Louis H. Clerf.
Surgical.
John B. Flick.

K 2 JEFFERSON HOSPITAL
(10th and Sansom Streets)

Curtis Clinic
(1015 Walnut Street)

Auditorium, 12th Floor

(Capacity, 170)

9:00– 9:20 A Phase of Arthritis.
Abraham Cohen.
9:20–9:40 Dermatological Aspects of Syphilis.
Abram Strauss.
9:40–10:00 Syphilis from the Urologist's Standpoint.
Stanley Q. West.
10:00–10:20 Neurological Aspects of Syphilis.
C. Fred Becker.
10:20–10:40 Medical Aspects of Syphilis.
Jacob Cahan.
10:40–11:00 Syphilis in Obstetrics.
Thaddeus L. Montgomery.
11:00–11:20 Treatment of Congenital Syphilis.
John Coppolino.
11:20–11:40 Occlusive Vascular Disease, Differential Diagnosis and Treatment.
David W. Kramer.
11:40–12:00 Larosidin in the Treatment of Peptic Ulcer.
John T. Eads.

K 3 JEFFERSON MEDICAL COLLEGE
(1025 Walnut Street)

(Capacity, 75)

Department of Pharmacology, Room 420

9:00–10:00 Demonstration.
Action of Drugs on Small Intestine.
The Effect of Some Hormones upon the Uterus and Ovaries of the Cat.
Charles M. Gruber and John T. Brundage.

Department of Pathology, Auditorium

10:00–11:00 Demonstration and Discussion.
The Shock Syndrome: Its Genesis and Associated Pathology.
Virgil H. Moon.

Wednesday, May 1, 1935 (Continued)

Department of Physiology, Room 410

11:00–12:00 Demonstration.
Some Gastro-intestinal Reflexes.
J. Earl Thomas and Joseph O. Crider.

K 4 **JEFFERSON HOSPITAL**
(10th and Sansom Streets)
Second Floor Medical
(Capacity, 15)

11:00–12:00 Ward Walk.
Ross V. Patterson.

L 1 **PENNSYLVANIA HOSPITAL**
(Entrance on 8th Street, halfway between Spruce and Pine Streets)
Hospital Chapel
(Capacity, 200)

Albert W. Bromer presiding

Symposium on Rheumatic Fever

9:00– 9:40 The Results of Four Years' Experience in the Treatment of Rheumatic Fever with Intravenous Streptococcus Vaccination.
Albert W. Bromer, New York, N. Y.

9:40–10:20 The Treatment of Children Under Eight Years of Age, with Rheumatic Heart Disease, with Intravenous Streptococcus Vaccination.
Francis Q. Thorp and D. Stewart Polk.

10:20–11:00 Cardiac Pain with Special Reference to its Causes in Rheumatic Fever.
Louis B. Laplace.

11:00–12:00 The Reaction of the Circulation to Exercise.
David P. Barr, St. Louis, Mo.

9:00– 1:00 P.M. The Library of the Pennsylvania Hospital, which is the first Medical Library of this country, will be open from 9:00 until 1:00 daily. Dr. Francis R. Packard is in charge of arranging this exhibit.

L 2 **PENNSYLVANIA HOSPITAL**
(Entrance on 8th Street, halfway between Spruce and Pine Streets)
Surgical Clinic
(Capacity, 200)

William D. Stroud presiding

Cardiovascular Symposium

9:00– 9:40 The Effects of Acetyl-B-Methylcholin on Paroxysmal Tachycardia and Peripheral Vascular Disease.
John A. Reisinger.

Wednesday, May 1, 1935 (Continued)

9:40–10:10 Whole Leaf Digitalis as Compared to its Glucosides in the Treatment of Cardiovascular Disease.
William D. Stroud.

10:10–10:40 Verodigen, a Digitalis Glucoside.
Joseph B. Vander Veer.

10:40–11:00 Digitaline Nativelle, a Digitalis Product.
D. W. Leik.

11:00–12:00 The Treatment of Cardiovascular Syphilis.
John H. Stokes and Associates.

L 3 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Ward Rounds

1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

9:00–10:00 Wards 3 and 4.
David L. Farley and Associates.

L 3b

9:00–10:00 Wards 1 and 4.
Thomas McCrae, Robert P. Regester and Associates.

Two above groups will consolidate for balance of program.

Ayer Clinical Laboratory

(Capacity, 24)

10:00–11:00 Clinicopathological Conference.
John T. Bauer.
Discussion, opened by Edward B. Krumbhaar.

Outpatient Department

11:00–11:30 Diabetes Clinic Demonstration.
Garfield G. Duncan.

11:30–12:00 The Administration of a Hospital Outpatient Department.
Samuel Bradbury.

Thursday, May 2, 1935

A 1 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Catherwood House
(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

9:00–12:00 Combined Clinic on Non-Specific Infections of the Lung.
John C. Gittings, Ralph D. Bromer, Edward H. Campbell, Gabriel Tucker, Irving J. Wolman, and Mitchell I. Rubin.

A 2 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Ward Walk
(Entrance, Bainbridge Street below 18th)

(Capacity, 10)

9:00–10:20 Ward Walk.
John P. Scott.

A 3 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease
(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

10:30–11:00 Demonstration by Charts of Reaction to Intramuscular Injection of Whole Human Blood.
Milton Rapoport.

11:00–11:30 Demonstration of a Health Appraisal.
Howard C. Carpenter.

11:30–12:00 Congenital Heart Disease.
Rachel Ash.

B 1 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

9:00– 9:20 Serum Phosphatase in the Differential Diagnosis of Jaundice.
Maurice Rothman.

9:20– 9:40 Takata Reaction in Hepatic Disease.
Henry Tumen.

Thursday, May 2, 1935 (Continued)

9:40–10:20 Clinic on Diseases of the Liver.
A. M. Snell, Rochester, Minn.

10:20–11:00 A Demonstration of the Diagnostic and Therapeutic Methods in the Allergic Diseases, with Special Reference to the Unusual.
H. B. Wilmer, John Murphy and Merle M. Miller.

11:00–11:20 Hypochloremia, Alkalosis with Azotemia and Dehydration.
John Eiman and Walter G. Karr.

11:20–12:00 Clinicopathological Conference.
Eugene Case and Members of Medical Staff.

B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

9:00– 9:40 Results of Neurosurgical Operations.
Francis C. Grant.

9:40–10:10 Pneumocranium in the Treatment of Character Changes in Children.
William Drayton.

10:10–10:40 Acute Disseminated Encephalomyelitis with Motion Pictures, Case Histories and Neuropathological Specimens.
Fred H. Leavitt.

10:40–11:10 Radiculitis and Neuritis: Its Diagnosis and Treatment.
Joseph C. Yaskin.

11:10–11:40 Treatment of Neurosyphilis: Case Demonstration.
Clarence A. Patten.

11:40–12:00 Cases Illustrating Maxillofacial Surgery.
Robert Ivy.

B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Assemble at Private Admissions' Desk

Demonstrations and Ward Clinics

(Capacity, 15)

9:00–10:00 Demonstration of Laboratory Procedures in the Diagnosis of Functional Disturbances of the Generative Tract.
Charles Mazer, A. J. Ziserman, and Adele Yamroz.

10:00–11:00 Ward Rounds.
George Morris Piersol.

11:00–12:00 Cardiovascular Diseases.
George C. Griffith.

Thursday, May 2, 1935 (Continued)

C 1 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Auditorium, 3d Floor, Medical Building

(Capacity, 250)

9:00– 9:45 The Brain in General Infections and Toxemias.
Nathaniel W. Winkelman.

9:45–10:30 Atrophy of the Frontal Lobes and Reversion to Infantile Behavior.
Walter Freeman, Washington, D. C.

10:30–11:15 Clinico-psychiatric Conference: Functional Disturbances of the Gastro-intestinal Tract.
Edward Weiss and O. Spurgeon English.

11:15–12:00 Anxiety States with Special Reference to Hyperventilation.
William J. Kerr, San Francisco, Calif.

C 2 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Surgical Amphitheatre, 3d Floor, Hospital

(Capacity, 100)

9:00– 9:30 A Consideration of Sinus Disease with Special Reference to the Cause of Headache.
Robert F. Ridpath.

9:30–10:00 Deafness from the Economic and Social Viewpoints.
Matthew S. Ersner.

10:00–10:30 Feet in their Relationship to Some Problems of the Internist.
John Royal Moore.

10:30–11:00 Studies on the Physiological Effects of Fever Produced by Physical Means.
Frank H. Krusen.

11:00–12:00 The Surgical Management of Esophageal Diverticulum.
W. Wayne Babcock and Chevalier Jackson.

C 3 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

X-Ray Museum, 6th Floor, Medical School Building

(Capacity, 50)

9:00–10:00 Hodgkin's Disease.
Clinical Aspects.
Barton R. Young.
Radiology.
W. Edward Chamberlain.
Pathology.
Frank W. Konzelmann.

Thursday, May 2, 1935 (Continued)

10:00–10:30 Diseases of the Breast.
W. Emory Burnett.

10:30–11:00 The Diagnosis of Malignant Disease with a Discussion of the Needle Biopsy.
Frank W. Konzelmann and Barton R. Young.

C 4 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Medical School Building, Room 502

(Capacity, 50)

11:00–12:00 The Nature and Clinical Applications of Bacteriophage Therapy.
John A. Kolmer.

C 5 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Outpatient Department, 2d Floor, Medical School Building

(Capacity, 20)

11:00–12:00 Demonstration of Retinal Changes in Medical and Neurological Conditions by Means of the Multiocular Ophthalmoscope.
Walter I. Lillie and Glen G. Gibson.

C 6 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

(Unlimited—No Tickets Required)

11:00–12:00 Demonstrations and Exhibits in Various Departments of the Hospital and Medical School—Special Hospital Program will be available.

D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Medical Clinic

(Capacity, 175)

9:00– 9:45 Syphilitic Heart Disease.
John H. Musser, New Orleans, La.

9:45–10:30 Clinic on Peripheral Vascular Disease with Demonstration of Suction and Pressure Apparatus.
Lewis H. Hitzrot.

10:30–11:15 Clinic on Pulmonary Cases.
Simon S. Leopold.

Thursday, May 2, 1935 (Continued)

11:15–11:30 The Results of Treatment in a Case of Addison's Disease.
Henry U. Hopkins.
11:30–12:00 Clinic on Diabetic Cases.
Francis D. W. Lukens.

D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(34th and Spruce Streets)

Agnew Clinic

(Capacity, 225)

9:00– 9:30 Small Intestinal Intubation: Its Value in the Study of Drug Actions.
William Osler Abbott.
9:30–10:30 Diagnosis and Treatment of Hypophyseal and Parahypophyseal Lesions.
Charles H. Frazier.
10:30–11:30 Clinic on Gall Bladder Disease. Correlation of Clinical Biliary Drainage and Cholecystographic Observations.
T. Grier Miller and E. P. Pendergrass.
11:30–12:00 Clinic on Cardiac Cases.
Charles C. Wolferth.

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a
9:00–10:30 Ward B.
Edward Rose.

D 3b
9:00–10:30 Ward D.
Richard A. Kern.

D 3c
9:00–10:30 Pepper Ward.
Isaac Starr, Jr.

Three above groups will alternate for the three following sets of demonstrations

Demonstrations in Maloney Clinic

10:30–11:00 8th Floor.
Relation between Adrenals, Pituitary Body and Diabetes Mellitus.
C. N. H. Long and Staff.
6th Floor, Department of Biophysics.
Use of Short Wave Diathermy in Internal Medicine.
D. W. Bronk and J. P. Herbey.
3d Floor, Gastro-intestinal Department.
Clinical Studies of Small Intestine.
T. Grier Miller and Staff.

Thursday, May 2, 1935 (Continued)

11:00–11:30 Room 218.
Immunity in Diabetes.
Russell Richardson.
Room 709.
Complement Fixation in Amoebiasis: Nature of Test; Value in Acute and Chronic States; Value of Cultural, Wet Smear and Complement Fixation Methods.
James S. Forrester.
Room 709.
New Method for Discovery of Sickle Cells in the Blood: Method to Discover the Trait that Develops Sickle Cells; Method for Permanent Films; Some Clinical Data.
James S. P. Beck.
Room 701.
Colorimetric Readings by the Method of Optical Filters (Photronic Cells): Determination of Hemoglobin, Blood Sugar, Phosphates, etc.; New Procedure for the Measurement of Serum Volume.
F. William Sunderman.

11:30–12:15 Room 311, Robinette Foundation.
Demonstration of the Use of Chest Leads in Electrocardiography. This demonstration will be of interest only to those with some knowledge of Clinical Electrocardiography.
Room 801.
Demonstration of the Enzyme Accelerating the Up-take of CO_2 by the Blood.
W. C. Stadie.
5th Floor.
Inspection of Department of Physiotherapy. Discussion of various procedures.
Josef B. Nylin.

D4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL BUILDING

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

9:00– 9:15 The Absorption of Sodium Tetraiodophenolphthalein from the Normal and Damaged Gall Bladder.
Julian Johnson.

9:15– 9:30 Measurement of Spinal Shock.
G. P. McCouch, Joseph Hughes, W. J. Snape and W. B. Stewart.

9:30– 9:45 The Effect of Oxygen in the Prevention of Liver Necrosis Induced by Volatile Anaesthetics.
S. Goldschmidt, I. S. Ravdin and Balduin Lucké.

9:45–10:00 The Bile in Biliary Tract Disease.
I. S. Ravdin, C. G. Johnson and C. Riegel.

10:00–10:20 The Emptying Time of the Stomach of the Dog before and after Gastric Operations.
C. G. Johnson, I. S. Ravdin and E. P. Pendergrass.

10:20–12:00 (*a*) Demonstrations in the Departmentment of Physiology:

Thursday, May 2, 1935 (Continued)

Room 126

(1) Secretion of the Liver as Indicated by Dyes.
R. Höber.

Room 34

(2) Penetration of O_2 into the Skin in Man.
S. Goldschmidt and Bartgis McGlone.

Room 136

(3) Optical Method for more Accurate Estimation of Systolic, Diastolic and Dicrotic Wave Pressures in Man.
H. C. Bazett and Louis B. Laplace.

(*b*) Demonstrations in the Department of Research Surgery:
(1) Small Intestinal Fistulae.
(2) Biliary Tract Fistulae.
(3) Subcutaneous Kidney.

There will also be demonstrations open to inspection from 9:00 to 12:00 in the Departments of Pathology, Bacteriology and Research Surgery.

E 1 LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Amphitheatre

(Capacity, 100)

9:00– 9:30 Medical Affections of the Biliary System.
Frank Weigand.

9:30–10:00 Cirrhosis of the Liver: Correlation of Experimental and Clinical Findings.
Jesse L. Bollman, Rochester, Minn.

10:00–10:30 The Indications for and Surgical Treatment of Biliary Tract Affections.
George P. Muller and Gilson Colby Engel.

10:30–11:00 The Diagnosis and Medical Management of Peptic Ulcer.
Daniel B. Pierson, Jr.

11:00–11:30 Bleeding Ulcer.
James H. Sterner.

11:30–12:00 Surgical Types of Ulcer and their Treatment.
Damon B. Pfeiffer.

E 2 LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Research Institute

(Capacity, 50)

9:00– 9:30 Specimens and Discussion of Retroperitoneal Tumors.
Clark E. Brown.

9:30–10:00 The Issues at Stake in the Grading of Tumors.
Stanley P. Reimann

Thursday, May 2, 1935 (Continued)

10:00–10:30 The Metastases of Carcinoma of the Stomach, with Especial Reference to Krukenberg's Tumor.
Clark E. Brown.

10:30–11:00 High Spots in Sulphur Metabolism.
Grace Medes.

11:00–11:30 The Toxicity of Certain Explosives Used in Industry.
Clark E. Brown.

11:30–12:00 Choice of Media for Illustrating Medical Papers.
Mrs. Wm. B. McNett.

E 3 LANKENAU HOSPITAL

(Corinthian and Girard Avenues)

Men's Medical Ward, Second Floor

(Capacity, 15)

11:00–12:00 Ward Rounds.
Frederick L. Hartmann.

F HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Elkins Amphitheatre, 3d Floor

(Capacity, 200)

9:00– 9:30 Neurological Clinic.
Edwin A. Steinhilber.

9:30–10:15 Hypertensive Cardiovascular Disease.
G. Harlan Wells.

10:15–10:45 Hypothyroidism.
Roger I. Lee, Boston, Mass.

10:45–11:15 Modern Treatment of Syphilis: Illustrated by Selected Cases.
C. Walter Clarke, New York, N. Y.

11:15–12:00 Clinicopathological Conference.
Grant O. Favorite.

G 1 PHILADELPHIA GENERAL HOSPITAL

(34th Street below Pine)

Clinical Amphitheatre

(Capacity, 250)

9:00– 9:30 Unilateral Non-tuberculous Bronchopneumonia of Long Duration.
David Riesman.

9:30–10:30 Syphilitic Heart Disease.
(*a*) Prevailing Status.
(*b*) Musical Murmurs.
(*c*) Syphilitic Myocarditis.
(*d*) Syphilitic Pericarditis.
Thomas M. McMillan, Samuel Bellet and Benjamin Gouley.

Thursday, May 2, 1935 (Continued)

10:30–11:00 Intestinal Tuberculosis.
Russell S. Boles and J. Gershon Cohen.

11:00–11:30 Closed Pneumolysis Supplementary to Artificial Pneumothorax in Pulmonary Tuberculosis.
George Willauer and David A. Cooper.

11:30–12:00 Factors Concerned in the Variations in Tolerance in Digitalis.
Samuel Bellet.

G 2 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Medical Section Building

(Capacity, 15)

9:00–10:00 Ward Walk.
Thomas Klein.

H 1 PRESBYTERIAN HOSPITAL
(39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

Symposium on Diabetes

9:00–10:00 Clinic on Diabetes.
Elliott P. Joslin, Boston, Mass.

10:00–10:20 Insulin Sensitivity.
Merle M. Miller.

10:20–10:40 Allergic Manifestation of Epidermophytosis in Diabetes.
Herbert T. Kelly.

10:40–11:00 Diabetes in Pregnancy.
Ford A. Miller.

11:00–11:20 Dental Care of the Diabetic.
James Aiguier, D. D. S.

11:20–12:00 Simplified Diet Calculation for the Diabetic.
Joseph T. Beardwood, Jr., and Henrietta Pribnow.

H 2 PRESBYTERIAN HOSPITAL
(39th Street and Powelton Avenue)

Ladies' Aid Room

(Capacity, 65)

9:00– 9:30 Treatment of Empyema.
Henry P. Brown and Orville King.

9:30–10:00 Huge Suprarenal Tumor.
George M. Laws.

10:00–10:30 Nephroptosis.
Joseph C. Birdsall.

Thursday, May 2, 1935 (Continued)

10:30–12:00 Clinical-Pathological Conference:
Renal Calculi.
Bilateral Reduplication of Kidneys.
Congenital Megalo-ureter.
Renal Tuberculosis.
Teratoma Testis.
Joseph C. Birdsall, Francis Harrison and Kenneth E. Fowler.

H 3 PRESBYTERIAN HOSPITAL
(39th Street and Powelton Avenue)

Medical Ward

(Capacity, 15)

9:30–10:30 Ward Rounds.
George C. Griffith.

At 10:30 those making ward rounds may join the Clinical-Pathological Conference in the Ladies' Aid Room.

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL
(111 North 49th Street)

Auditorium

(Capacity, 250)

9:00– 9:20 Introduction.
Edward A. Strecker.
9:20– 9:40 Medical Aspect of the Neuroses.
Lauren H. Smith.
9:40–10:00 Psychoanalytic-Medical Relationships.
Kenneth E. Appel.
10:00–10:20 Physiological Factors in Psychiatric Research.
Harold D. Palmer.
10:20–10:40 The Response of the Spinal Cord to Two Stimuli.
Joseph Hughes.
10:40–11:00 Post-Encephalitic Behavior Disorders.
Earl D. Bond.
11:00–12:00 Historical Exhibit (Library of the Parent's Council). Books and Curiosa Relating to Psychiatry.
Clifford B. Farr.
Inspection of the Institute, Laboratories and Franklin School.

K 1 JEFFERSON HOSPITAL
(10th and Sansom Streets)

Clinical Amphitheatre
(1020 Sansom Street)

(Capacity, 250)

9:00– 9:40 Diathermy Versus Vaccinal Therapy in Chorea.
Edward L. Bauer.
9:40–10:00 Hormonal Studies in Twins.
Aaron Capper.

Thursday, May 2, 1935 (Continued)

10:00–11:00 Nephrolithiasis:
Symptoms and Diagnosis.
Willard H. Kinney.
Treatment.
Thomas C. Stellwagen.

11:00–11:30 Digitalis Therapy.
Ross V. Patterson.

11:30–12:00 Variations in Symptomatology and Physical Signs in Acute Coronary Thrombosis.
Henry K. Mohler.

K 2 JEFFERSON HOSPITAL

(10th and Sansom Streets)

Curtis Clinic
(1015 Walnut Street)

Auditorium, 12th Floor

(Capacity, 170)

9:00– 9:20 Infection in Gall Bladder Disease.
Guy M. Nelson.

9:20– 9:40 Surgical Treatment of Pulmonary Tuberculosis.
George Willauer.

9:40–10:00 The Male Sex Hormone.
James McCahey.

10:00–10:15 Diagnosis of Hay Fever.
J. Alexander Clarke, Jr.

10:15–10:30 Routine Management of Asthma.
J. Alexander Clarke, Jr.

10:30–10:45 Treatment of Laryngeal Tuberculosis.
Robert M. Lukens.

10:45–11:00 Recent Advances in Medical Treatment of Pulmonary Tuberculosis.
Burgess L. Gordon.

11:00–11:15 Oxygen Therapy in Medicine.
Robert B. Nye.

11:15–11:30 Discussion and Presentation of Cases of Essential Hypertension.
Reynold S. Griffith.

11:30–12:00 A Tumor Clinic: Presentation of Neoplasms of Gastro-intestinal Tract.
Edward J. Klopp, David W. Kramer, Willis F. Manges, William S. Newcomet, Bruce L. Fleming and George E. Marcil.

K 3 JEFFERSON MEDICAL COLLEGE

(1025 Walnut Street)

Auditorium

(Capacity, 75)

9:00–10:00 Clinicopathological Conference.
S. A. Loewenberg and Virgil H. Moon.

Thursday, May 2, 1935 (Continued)

10:00–10:30 Renal Tuberculosis: Study and Diagnosis; Pathological and Bacteriological Phase.
Carl J. Bucher.

10:30–11:00 Urological and Roentgen Ray Phase. (Lantern Slides.)
Theodore R. Fetter.

11:00–12:00 Recent Advances in Treatment of Diseases of the Skin.
Frank C. Knowles and Edward F. Corson.

K 4 JEFFERSON HOSPITAL

(10th and Sansom Streets)

Second Floor Medical

(Capacity, 15)

11:00–12:00 Ward Walk.
Fred J. Kalteyer.

L 1 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Hospital Chapel

(Capacity, 200)

William D. Stroud presiding

Cardiovascular Symposium

9:00– 9:45 The Electrocardiogram as an Aid to the Diagnosis and Prognosis of Acute Coronary Occlusion.
Joseph B. Vander Veer.

9:45–10:45 Acute Pulmonary Edema in Heart Disease.
Paul D. White, Boston, Mass.

10:45–11:30 Coronary Disease, Including Angina Pectoris.
William D. Stroud.

11:30–12:00 X-Ray Findings in Calcification of the Heart Valves and Pericardium.
Paul A. Bishop.

9:00– 1:00 P.M. The Library of the Pennsylvania Hospital, which is the first Medical Library of this country, will be open from 9:00 until 1:00 daily. Dr. Francis R. Packard is in charge of arranging this exhibit.

Thursday, May 2, 1935 (Continued)

L 2 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Surgical Clinic

(Capacity, 200)

Thomas McCrae presiding

Symposium on New Growths of the Lung

9:00– 9:45 The Diagnosis of New Growths of the Lung from the Bronchoscopic Standpoint.
Louis H. Clerf.

9:45–10:30 The Diagnosis and Treatment of New Growths of the Lung from the Roentgenographic Standpoint.
Paul A. Bishop.

10:30–11:15 The Diagnosis and Treatment of New Growths of the Lung from the Standpoint of the Internist.
Robert P. Regester.

11:15–12:00 The Surgical Treatment of New Growths of the Lung.
John B. Flick.

L 3 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Ward Rounds
1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

9:00–10:00 Wards 3 and 4.
David L. Farley and Associates.

L 3b

9:00–10:00 Wards 1 and 4.
Thomas McCrae, Robert P. Regester and Associates.

Two above groups will consolidate for balance of program

Ayer Clinical Laboratory

(Capacity, 24)

10:00–11:00 Clinicopathological Conference.
John T. Bauer.

Outpatient Department

11:00–11:30 Adult Heart Clinic Demonstration.
Thomas M. McMillan.

11:30–12:00 The Administration of a Hospital Outpatient Department.
Samuel Bradbury.

Friday, May 3, 1935

A 1 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Catherwood House
(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

9:00–10:00 Artificial Pneumothorax in Tuberculosis in Children.
F. Maurice McPhedran.

10:00–11:00 Enuresis as a Psychiatric Problem.
Frederick H. Allen.

11:00–12:00 Urological Lesions in Upper Urinary Tract in Children.
Albert E. Bothe.

A 2 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Ward Walk
(Entrance, Bainbridge Street below 18th)

(Capacity, 10)

9:00–10:20 Ward Walk.
John C. Gittings.

A 3 CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease
(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

10:30–11:00 Application of the Refractometer to Clinical Material.
Horace L. Hodes.

11:00–11:30 Congenital Pulmonary Malformations.
Irving J. Wolman.

11:30–12:00 Demonstration of Technique of Virus Culture.
Arthur D. Waltz and Alice Chenoweth.

B 1 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

9:00– 9:40 Clinic on Gastric Ulcer.
Sara Jordan, Boston, Mass.

Friday, May 3, 1935 (Continued)

9:40–10:20 Puzzling Types of Indigestion.
Walter Alvarez, Rochester, Minn.

10:20–11:00 Gastro-enterological Conference.
H. L. Bockus, W. Estell Lee, Karl Kornblum and Eugene Case.

11:00–11:15 Experience with Spinal Anaesthesia in Gastro-intestinal and Intra-abdominal Surgery.
W. Estell Lee and Orville King.

11:15–11:30 Roentgen Diagnosis of "Milk of Calcium" Bile.
Karl Kornblum.

11:30–11:50 Abdominal Symptomatology in Diabetic Acidosis.
Joseph T. Beardwood, Jr.

11:50–12:00 A Case of Lead Poisoning of Unusual Origin.
John H. Willard.

B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

9:00–9:20 Presentation of a Family with Hemophilia.
H. Leon Jameson.

9:20–10:10 The Clinical Significance of Venous Pressure Estimation.
George C. Griffith and J. Roderick Kitchell.

10:10–11:00 Factors Influencing Sedimentation Test.
Fred Boerner.

11:00–12:00 Esophagoscopic Observations in Diseases of the Esophagus.
Gabriel Tucker.

B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

Assemble at Private Admissions' Desk

Demonstrations and Ward Clinics

(Capacity, 15)

9:00– 9:45 A New Test for the Phagocytic Power of Whole Blood.
Fred Boerner and Stuart Mudd.

9:45–10:30 Presentation of Material from the Chest Clinic.
Richard T. Ellison.

10:30–11:15 Ward Rounds.
B. J. Alpers.

11:15–12:00 Bedside Observations in Cardiovascular Disease:
(*a*) Determination of Heart Size.
(*b*) Determination of Arteriosclerosis.
Hugh Miller.

Friday, May 3, 1935 (Continued)

C1 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Auditorium, 3d Floor, Medical Building

(Capacity, 250)

9:00– 9:15 An Analysis of 100 Cases of Hemoptysis from the Bronchoscopic Clinic.
N. M. Levin.

9:15– 9:45 Hiatal Hernia of the Stomach and Congenital Short Esophagus.
C. L. Jackson and Albert K. Merchant.

9:45–10:00 A Method of Directly Recording Bronchial Contractions.
M. P. Ellis and Alfred E. Livingston.

10:00–10:30 Gastroscopy with Special Reference to the Flexible Gastroscope.
C. L. Jackson and W. A. Swalm.

10:30–11:00 The Surgical Treatment of Pulmonary Suppuration.
W. Emory Burnett.

11:00–11:30 Bronchoscopy in Acute and Chronic Infections of the Trachea and Bronchi.
Chevalier Jackson.

11:30–12:00 The Rôle of Oral Spirochetes and Associated Anaerobes in Pyorrhea and Pulmonary Abscess. (Motion Picture Demonstration.)
Arthur Q. Penta.

C2 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

Surgical Amphitheatre, 3d Floor, Hospital

(Capacity, 100)

9:00– 9:15 Studies on Pituitary Extracts.
Edward Larson.

9:15– 9:30 Pituitary Basophilism.
Michael G. Wohl and Barton R. Young.

9:30–10:00 Agranulocytosis and the Leukemias.
W. Edward Chamberlain and Louis Soloff.

10:00–11:00 Etiology and Management of Various Forms of Anemia.
Maurice B. Strauss, Boston, Mass.

C3 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

X-Ray Museum, 6th Floor, Medical School Building

(Capacity, 50)

9:00– 9:30 The Treatment of Cardiovascular Syphilis.
Jacques Guequierre.

9:30– 9:45 Coarctation of the Aorta.
Morris Kleinbart.

Friday, May 3, 1935 (Continued)

9:45–10:15 The Heart and Athletics.
Hugo Roesler.
10:15–11:00 Low Back Pain.
W. Edward Chamberlain and John Royal Moore.

C 4 TEMPLE UNIVERSITY MEDICAL SCHOOL AND HOSPITAL

(3400 North Broad Street)

(Unlimited—No Tickets Required)

11:00–12:00 Demonstrations and Exhibits in Various Departments of the Hospital and Medical School—Special Hospital Program will be available.

D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Medical Clinic

(Capacity, 175)

9:00– 9:30 The Treatment of the Attack in Paroxysmal Tachycardia and Other Clinical Uses of Derivatives of Choline. Case Demonstrations.
Isaac Starr, Jr.
9:30–10:00 Clinic on Agranulocytic Angina.
Thomas Fitz-Hugh, Jr.
10:00–10:45 Clinical Allergy.
Richard A. Kern.
10:45–11:30 Clinic on the Diagnosis and Treatment of Hypothyroid States.
Edward Rose.
11:30–12:00 Clinicopathological Conference.
Balduin Lucké and Medical Staff.

D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(34th and Spruce Streets)

Agnew Clinic

(Capacity, 225)

9:00–10:00 Clinic on Biliary Tract Disease.
I. S. Ravdin and Associates.
10:00–10:30 The Functions and Disorders of the Sympathetic Nervous System.
Detlev W. Bronk.
10:30–10:45 The Carotid Sinus Reflex in Patients with Hypertension.
George Gammon.
10:45–11:15 Diagnosis and Treatment of the Common Dermatoses.
Vaughn C. Garner.
11:15–12:00 Clinic on Ureteral Obstruction.
Alexander Randall.

Friday, May 3, 1935 (Continued)

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a

9:00–10:30 Ward B.
James E. Cottrell.

D 3b

9:00–10:30 Ward D.
Charles C. Wolferth.

D 3c

9:00–10:30 Pepper Ward.
Leon H. Collins, Jr.

Three above groups will alternate for the three following sets of demonstrations.

Demonstrations in Maloney Clinic

10:30–11:00 8th Floor.
Relation between Adrenals, Pituitary Body and Diabetes Mellitus.
C. N. H. Long and Staff.
6th Floor, Department of Biophysics.
Use of Short Wave Diathermy in Internal Medicine.
Detlev W. Bronk and J. P. Herby.
3d Floor, Gastro-intestinal Department.
Clinical Studies of Small Intestine.
T. Grier Miller and Staff.

11:00–11:30 Room 218.
Immunity in Diabetes.
Russell Richardson.
Room 709.
Complement Fixation in Amoebiasis: Nature of Test; Value in Acute and Chronic States; Value of Cultural, Wet Smear and Complement Fixation Methods.
James S. Forrester.
Room 709.
New Method for Discovery of Sickle Cells in the Blood: Method to Discover the Trait that Develops Sickle Cells; Method for Permanent Films; Some Clinical Data.
James S. P. Beck.
Room 701.
Colorimetric Readings by the Method of Optical Filters (Photronic Cells): Determination of Hemoglobin, Blood Sugar, Phosphates, etc.; New Procedure for the Measurement of Serum Volume.
F. William Sunderman.

11:30–12:15 Room 311, Robinette Foundation.
Demonstration of the Use of Chest Leads in Electrocardiography. This demonstration will be of interest only to those with some knowledge of Clinical Electrocardiography.

Friday, May 3, 1935 (Continued)

Room 801.

Demonstration of the Enzyme Accelerating the Up-take of CO_2 by the Blood.

W. C. Stadie.

5th Floor.

Inspection of Department of Physiotherapy. Discussion of various procedures.

Josef B. Nylin.

D 4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL BUILDING

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

9:00– 9:30 Possibilities of Use of Serum from Human Sources: (a) Pooled Normal Adult; (b) Convalescent; (c) From Hyperimmunized Donors, in Prevention and Treatment of Infectious Disease.

Stuart Mudd.

9:30–10:00 Recent Studies on Urine Formation.

A. N. Richards.

10:00–10:30 Carotid Sinus Reflexes: Their Rôle in the Regulation of Respiration and in the Action of Certain Respiratory Stimulants.

Carl F. Schmidt.

10:30–12:00 (a) Demonstrations in the Department of Bacteriology: Room 214.

(1) New Method of Preservation of Serum.

Earl W. Flosdorf.

(2) An Improved Phagocytic Method as a Measure of the Virulence of an Organism and of the Efficacy of Therapeutic Sera.

Fred Boerner and Stuart Mudd.

(3) Eagle Test for Syphilis.

Harry Eagle.

(4) Rough, Smooth and Filterable Variants of the Diphtheria Bacillus.

Harry E. Morton.

(b) Demonstrations in the Department of Pharmacology:

Room 164

(1) Carotid Sinus Reflexes Caused by Physical and Chemical Agents.

H. A. Royster, Jr., W. B. Test and Carl F. Schmidt.

(2) Demonstrations of Methods Used in the Direct Study of Glomerulus and Tubule in the Amphibian Kidney.

Arthur M. Walker, Hugh Montgomery and J. P. Hendrix.

There will also be demonstrations open to inspection from 9:00 to 12:00 in the Departments of Pathology, Bacteriology and Research Surgery.

Friday, May 3, 1935 (Continued)

E 1 LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Amphitheatre

(Capacity, 100)

9:00– 9:30 Choice of Cases for Various Types of Treatment in Pulmonary Tuberculosis.
Francis M. Pottenger, Monrovia, Calif.

9:30–10:00 Surgical Treatment of Tuberculosis.
George P. Muller.

10:00–10:30 Agranulocytosis.
Henry Jackson, Boston, Mass.

10:30–11:00 Diagnosis and Treatment of Head Trauma.
Clarence A. Patten.

11:00–11:30 Habitual Hyperthermia.
Hobart A. Reimann, Minneapolis, Minn.

11:30–12:00 Hematuria.
William H. Mackinney.

E 2 LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Men's Medical Ward, Second Floor

(Capacity, 15)

11:00–12:00 Ward Rounds.
Edward L. Bortz.

F HAHNEMANN MEDICAL COLLEGE AND HOSPITAL
(Broad Street above Race)

Elkins Amphitheatre, 3d Floor

(Capacity, 200)

9:00– 9:30 Diseases of the Hemopoietic System in Children.
C. S. Raue.

9:30–10:00 Juvenile Diabetes Mellitus.
William R. Williams.

10:00–10:30 Pernicious Anemia and Intravenous Liver Extract.
Dunne W. Kirby.

10:30–11:00 Chest Pain.
George D. Geckeler.

11:00–11:30 Atypical Leukemias.
Ernest B. Bradley, Lexington, Ky.

11:30–12:00 Clinicopathological Conference (Pediatric).
Carl C. Fischer and Russell Fischer.

Friday, May 3, 1935 (Continued)

G 1 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Auditorium

(Capacity, 200)

9:00– 9:45 Pericarditis:
(1) Observations on the Electrocardiographic Changes in Acute Variety.
(2) *a*—Acute and Tuberculous Varieties—Signs, Symptoms and X-Ray Findings.
b—Differentiation from Rheumatic Type.
(3) *a*—Basal Constricting Pericarditis (Pulmonary Artery).
b—Evidences to Show that the Tuberculous Variety Does Recover and Become Adhesive.
Thomas M. McMillan and Benjamin Gouley.

9:45–10:05 The Ability of the Heart to Recover Completely from Extreme Dilatation.
Louis B. Laplace.

10:05–10:35 A Comparative Study of Venous, Intraspinal and Arterial Pressures with Especial Reference to Failure of the Right Heart.
Harold F. Robertson.

10:35–11:05 Aneurysms of the Sinuses of Valsalva and Studies of the Interventricular Septum.
Benjamin Robinson.

11:05–11:25 Low Blood Urea.
Frank Leivy.

11:25–12:00 Some Unusual Phases of Rheumatic Fever.
Robert G. Torrey and R. P. Custer.

G 2 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Clinical Amphitheatre

(Capacity, 250)

9:00– 9:50 Arterial Hypertension.
Leonard G. Rowntree.

9:50–10:05 Fever Therapy:
(*a*) Gonorrheal Arthritis.
(*b*) Chorea.
Ferdinand Fetter.

10:05–10:35 The Clinical Application of the Various Methods of Investigating the Circulation of the Extremities.
David W. Kramer.

10:35–11:35 The Treatment of Diabetic Lesions of the Feet, with Especial Reference to Non-surgical Management.
Edward S. Dillon and Lewis H. Hitzrot.

11:35–11:45 Studies in Febrile Albuminuria.
John W. Welty.

11:45–12:00 Weil's Disease.
Kenneth E. Reynolds and R. E. Otten.

Friday, May 3, 1935 (Continued)

G 3 PHILADELPHIA GENERAL HOSPITAL

(34th Street below Pine)

Medical Section Building

(Capacity, 15)

9:00–10:00 Ward Walk.
Henry D. Jump.

H 1 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

9:00– 9:50 Diseases of the Adrenals.
David P. Barr, St. Louis, Mo.
9:50–10:20 Treatment of the Naevi.
William S. Newcomet.
10:20–11:00 Relation of Posture to Diagnosis.
William Bates and J. C. Howell.
11:00–12:00 Medical Clinic.
John B. Youmans, Nashville, Tenn.

H 2 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Ladies' Aid Room

(Capacity, 65)

9:00– 9:30 Orthopedic Care of Arthritis.
T. E. Orr.
9:30–10:30 Lumbar Ganglionectomy in Arthritis.
F. A. Bothe.
10:30–12:00 Clinical-Pathological Conference:
Multiple Myeloma.
Paul North.
Fibroblastoma of Frontal Lobe.
W. B. Cadwalader.
Congenital Tuberculosis.
Charles A. Fife.
Erythroblastosis Fetalis.
John P. Scott.

H 3 PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Children's Ward

(Capacity 15)

9:30–10:30 Ward Rounds.
John P. Scott.

At 10:30 those making ward rounds may join the Clinical-Pathological Conference in the Ladies' Aid Room.

Friday, May 3, 1935 (Continued)

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL
(111 North 49th Street)

No Program On Friday

K JEFFERSON HOSPITAL
(10th and Sansom Streets)

Clinical Amphitheatre
(1020 Sansom Street)

(Capacity, 250)

9:00–10:00 The Diagnosis and Treatment of Certain Diseases of the Esophagus.
Roentgen Ray
Willis F. Manges.
Esophagoscopic
Louis H. Clerf.
Surgical
Thomas A. Shallow.

10:00–11:00 Brain Tumor.
William Duane, Jr., Benjamin Weiss and Michael A. Burns.

11:00–11:20 Physiology of the Stomach in Relation to Ulcer.
J. Earl Thomas.

11:20–11:40 Surgical Aspect.
Edward J. Klopp.

11:40–12:00 Medical Aspect and Gastric Photography.
Martin E. Rehfuss.

L 1 PENNSYLVANIA HOSPITAL
(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Hospital Chapel

(Capacity, 200)

F. William Sunderman presiding

Symposium on Diabetes and Metabolic Abnormalities

9:00– 9:45 Diabetic Arteriosclerosis.
Edward S. Dillon.

9:45–10:30 Diabetic Acidosis with Especial Reference to Therapy.
F. William Sunderman.

10:30–11:15 Heart Muscle Efficiency in Metabolic Disorders.
Jonathan C. Meakins, Montreal, Que.

11:15–12:00 Interpretation of Renal Tests.
Joseph M. Hayman, Jr., Cleveland, Ohio.

9:00– 1:00 P.M. The Library of the Pennsylvania Hospital, which is the first Medical Library of this country, will be open from 9:00 until 1:00 daily. Dr. Francis R. Packard is in charge of arranging this exhibit.

Friday, May 3, 1935 (Continued)

L 2 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Surgical Clinic

(Capacity, 200)

Thomas McCrae presiding

9:00– 9:45 Duodenal Extract in the Treatment of Diabetes Mellitus.
Garfield G. Duncan.

9:45–10:30 Clinic on the Acute Abdominal Syndrome and Infections in Diabetes.
Edward H. Mason, Montreal, Que.

10:30–11:15 Clinic on Hypothyroidism.
Roger I. Lee, Boston, Mass.

11:15–12:00 Medical Clinic.
Thomas McCrae.

L 3 PENNSYLVANIA HOSPITAL

(Entrance on 8th Street, halfway between Spruce and Pine Streets)

Ward Rounds
1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

9:00–10:00 Wards 3 and 4.
David L. Farley and Associates.

L 3b

9:00–10:00 Wards 1 and 4.
Thomas McCrae, Robert P. Regester and Associates.

Two above groups will consolidate for balance of program

Ayer Clinical Laboratory

(Capacity, 24)

10:00–11:00 Clinicopathological Conference.
John T. Bauer.
Discussion, opened by John R. Paul, New Haven, Conn.

Outpatient Department

11:00–11:30 Allergy Clinic Demonstration.
James S. McLaughlin.

11:30–12:00 The Administration of a Hospital Outpatient Department.
Samuel Bradbury.

MINUTES OF THE MEETING OF THE BOARD OF REGENTS, PHILADELPHIA, DECEMBER 16, 1934 (*Continued*)

Upon motion by Dr. Barr, seconded and regularly carried, it was *Resolved,*

(1) That the name of the John Phillips Memorial Prize Committee be changed to the Committee on Fellowships and Awards.

(2) That a die be cast from a design herewith presented by the Committee for a medal to be awarded "For Achievement in Internal Medicine."

(3) That in order to make the series of Phillips medalists complete, medals be given to Dr. Avery and to Dr. Castle, the former recipients of the prize.

(4) That the John Phillips Memorial Medal of the American College of Physicians be awarded in 1935 to Professor Leo Loeb. In making this recommendation the Committee has in mind the rich accomplishment of a life time devoted to researches in the medical sciences and particularly Professor Loeb's recent investigations which have greatly extended our knowledge of the action of that hormone of the anterior pituitary gland whose injection produces the main symptoms of Graves' disease in animals.

During his approximately 40 years of active work Professor Loeb has contributed to many fields of general and experimental pathology. His first researches in 1895 concerned the transplantation of pigmented skin. This later developed into a study of the main factors underlying transplantations in general, and has more recently led to an analysis of organismal differentials and individuality in various life processes, including immunity.

Early studies of wound healing led to researches on the mechanism of growth, tissue culture and tissue formation in general and to the production of experimental "amebocyte tissue," which served as a model and which aided in the analysis of ameboid movement, tissue stereotropism and other factors active in wound healing and inflammatory processes.

These last investigations led to a study of the agglutinative processes underlying thrombosis and to the specific adaptations which exist between blood plasma and the factors accelerating and inhibiting coagulation of blood.

At a very early stage Professor Loeb undertook investigations in the pathological physiology of tumors, which have been continued during his many years of work. His well known pioneer researches on the transplantation of malignant tumors in animals made possible the study of heredity in tumors and the first quantitative determination of this factor.

Investigations concerning the relationship between hereditary factors and internal secretions in the origin of tumors led to a study of the internal secretions in the ovary and of the mechanism underlying the sex cycle, to an analysis of the functions of the corpus luteum and of the factors underlying placenta formation and the development of experimental placentomata.

In this connection Professor Loeb also studied the occurrence of far going parthenogenetic development of ova and of the formation of chorion epitheliomatous structures in the mammalian ovary and their relationship to the interpretation of certain tumors found in man.

The investigations concerning the sexual cycle led to an analysis of certain hormones of the anterior pituitary and their significance for the ovary and the thyroid gland.

While these have been the main lines of Professor Loeb's researches, he has also made important contributions on the analysis of the venom of Heloderma, upon certain factors underlying edema, on the urease occurring in amebocytes, the relations

between various cations and enzyme action and upon the intrauterine inoculation of microörganisms into the closed uterine cavity.

Since 1929 Professor Loeb has published a long series of papers upon the effects of injection of the thyroid influencing hormone of the anterior hypophysis. Through these important studies on experimental animals dealing especially with the increased mitotic activity of the thyroid cells, changes in iodine content of the thyroid gland, elevations of basal metabolism, circulatory changes and exophthalmos, it has been made clear that the symptoms of Graves' disease may be reproduced in mammals by the injection of this hormone.

(5) That letters be sent to Professors of Medicine and of Pediatrics, and to members of the Board of Regents, requesting recommendations for candidates for the Research Fellowship of the American College of Physicians, and that the form of recommendation be of the general type used by the National Research Council.

Dr. Luther F. Warren reported for the Committee on Extension of Postgraduate Education in the absence of Dr. F. M. Pottenger, Chairman. Dr. Warren explained that the specific matter on which the Committee was requested to report was a resolution passed by the Board of Regents at one of its April 1934, meetings, providing an investigation of the advisability of, and formulation of plans for, the closer organization and greater cohesion of our members in their particular communities or States, such as is done by the American College of Surgeons through sectional meetings, with the object of carrying extension postgraduate medical educational facilities to physicians in more remote locations. The Committee presented the recommendation that the Board of Regents shall encourage the Governors of the several States to have local clinical meetings, with the object of stimulating the purpose of the College. The adoption of the report was moved and seconded.

In the discussion that ensued, the following matters were pointed out: (1) the Chairman of the Board of Governors would be requested to inform the several Governors of the action of the Board of Regents; (2) State Medical Societies are carrying on an enormous amount of sectional work, and the College should not duplicate their efforts; (3) such meetings, as recommended by the Committee, would promote greater comradeship among the Fellows in each district, and make the College a little more tangible to them; (4) the recommendation is very broad and there should be much latitude given to members in the method of conducting these meetings; (5) that the plan is presented purely as an experimental one; (6) that the College might officially assist through the Executive Offices and even by financial aid, where justified.

Dr. Warren accepted an amendment to the resolution presented by Dr. White, and by unanimous vote, it was

Resolved, that the Board of Regents shall encourage the Governors of the several States, singly or in regional coöperation, to have local clinical meetings, with the object of stimulating the purposes of this College.

Dr. Charles F. Martin, Chairman of the Committee on Finance, presented the following report:

"(1) Income and Expenses, January 1, 1934, to November 30, 1934, with estimated income and expenses for the month of December 1934; (2) Budget Comparison, for expenditures and budget appropriations for 1934; (3) Cost Analyses for ANNALS OF INTERNAL MEDICINE, Volumes V, VI and VII; (4) Comparative Cost Analyses for the Annual Clinical Sessions, San Francisco, Montreal and Chicago (1932, 1933 and 1934).

"These statements have been prepared for you by the Executive Secretary. The feature of these reports is their prophetic accuracy. Added to this is the conscientious adherence to expenditures within the budgets.

"Your Committee has the honor to report a most satisfactory condition of the finances of the College during the past 11 months. The financial year terminates

December 31, so the time is not ripe for a complete detailed statement. The picture, however, is adequate. Features of interest in the report are: (1) maintenance of annual dues in excess of all expectation; (2) increase in initiation fees; (3) increase in Life Membership Fees (Secretary stimulated interest); (4) profit from sale of securities; (5) profitable operation of ANNALS—printers and advertising; (6) total excess of income over expenditures for year, $16,000.00.

"Your Committee regards it as a pleasant duty to congratulate the Executive Secretary, the Treasurer, and administration generally, and to express their unqualified appreciation of the management of the finances of the College—all the more remarkable in view of general business conditions.

"*Investments:* Your Committee believes in a more concrete designation of the funds of the College, and suggests:

"All moneys, securities and investments be included in the term, General Funds.

"Under this heading may be stipulated:

(1) Endowment Fund and any other restricted funds, which, with respect to capital, are not to be utilized for current expenses—though the interest may be added to the current account. This fund amounts to approximately $54,000.00.

(2) Free current or unrestricted funds, which may include the investment account, bank balances and any other cash or liquid assets. These total approximately $70,000.00.

"A scrutiny of present securities has suggested to your Committee the need of some change in the nature of the investments, more especially the sale of some of the municipal bonds. In practically every instance this may be achieved with some profit.

"In consideration of further investments, your Committee asks the endorsement of the Board of Regents on the policy of investing some of the College moneys, not exceeding 15 per cent, in carefully selected stocks, as necessary protection versus possible inflation.

"It further recommends the purchase of some Canadian securities, both bonds and stocks, the latter not to exceed a proportion of 15 per cent of the total Canadian investments.

"In conclusion, the Committee asks approval of the tentative budget of the Executive Secretary and the Treasurer for 1935 (in which income is estimated at $68,000.00 and expenditures at $52,125.00) until such time in April as the Board receives more detailed figures at its Annual Session.

Respectfully,

JAMES ALEX. MILLER
ROGER I. LEE
C. F. MARTIN, *Chairman*"

On motion by Dr. Martin, seconded by Dr. Herrick, and regularly carried, it was *Resolved*, that the report of the Committee on Finance be approved.

Dr. William D. Stroud, Treasurer, spoke briefly to the effect that the College should be much encouraged by the financial situation of its investments, the manner in which the funds are being collected and the careful way in which those in charge of expending funds have stayed within their budgets.

Dr. Maurice C. Pincoffs, Editor, and Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported that he had held no formal meeting of his Committee owing to the fact that local business in Baltimore had prevented his arriving in the City sufficiently in advance of the Regents' meeting. He said he had nothing in particular to report, other than such reactions as he receives, for the most part favorable, to the publication policy for the journal, and occasional communications suggesting the advisability of adding more clinical articles. Bedside clinical articles

are the most difficult to obtain. There is a great field for someone who will write interestingly about clinical disease rather than the measurement of disease. The ANNALS has been running on a satisfactory basis; to expand the ANNALS to some additional fields is a matter open for discussion in the Board of Regents. Dr. Pincoffs expressed the desire to have suggestions and criticisms from the Board. The fact that the journal is carrying itself financially may make expansion feasible, such as the inauguration of some particular instructional feature or features.

On motion by Dr. James Alex. Miller, seconded by Dr. James B. Herrick, and regularly carried, it was

Resolved, that the Board of Regents express its tremendous satisfaction with the work of the Editor, and extend to him their congratulations and thanks.

Dr. James Alex. Miller, Chairman of the Committee on Public Relations, presented the following matters that had been referred to his Committee:

(1) "Twenty paragraphs on Coöperative Hospital Service" from the President of the Allegheny (Pa.) County Medical Society, with the suggestion that this body may be willing to give an opinion thereon.

Dr. Miller expressed the opinion that the College is not in a position to know of such local experiments, and that there is actually nothing to act on.

On motion by Dr. Miller, seconded by Dr. Pepper, and regularly carried, it was

Resolved, that the College acknowledge receipt of the material, express its appreciation and state that it is not in a position to express approval or disapproval of such local experiments.

(2) A communication from Dr. William Henry Walsh (Fellow), of Chicago, setting forth a plan by which the College might take an active part in an organized way in familiarizing itself with what is going on in the field of hospital practice and medical economics, and setting forth also a definite proposition for a council on professional service.

(3) A communication to Dr. James H. Means, suggesting that the College should take some definite stand on medical economic problems, citing the fact that three members of our Board of Regents are on the Medical Advisory Board of President Roosevelt's Committee on Economic Security.

Dr. Miller stated that the Medical Advisory Board, on which Dr. Walter L. Bierring (Regent), Dr. George Morris Piersol (Regent), Dr. James D. Bruce (Governor) and Dr. Stewart R. Roberts (Fellow) and himself (Officer) are among the members, had sat in conference with President Roosevelt on an interesting discussion and review of the present situation, in which some of the progress that has been made in Washington was laid before the Board.

Dr. Miller suggested that the Regents of the College consider if the College has any function in this situation. He reported that there is now very great likelihood of better reaction toward the matter of medical economics and that the American Medical Association has been requested and has accepted the responsibility of assisting in working out some solution to some of the economic problems. It was felt that the American Medical Association has adopted an interested and constructive attitude in this matter. The question has arisen as to what action the College should take, if any. The Committee on Public Relations felt that the College should do nothing that would embarrass in the least degree the new relations that have been established with the American Medical Association, and that any initiative on the part of the College should be in the direction of coördination and in harmony with their program.

The Committee voted to suggest to the Board of Regents the possibility of using the ANNALS OF INTERNAL MEDICINE as a medium of regular distribution or dissemination of knowledge about these economic problems, working up a definite number of articles on various selected subjects. These articles should not in any way commit the College to any policy, but be purely informative and educational, present-

ing the problem, stating what has been done in this and other countries and, in general, informing our members of the various features of the situation. The Committee has consulted with the Editor, Dr. Pincoffs, who is sympathetic to the idea. The College might think it worth while to ask other coöperation in this matter, to start with a preparatory explanation of what the object is and then to have an advisory committee to the Editor to collect the articles and publish them in a definite series. It is possible that after a year of education in this matter, the whole situation could be definitely crystallized in one or two outstanding papers on our clinical program for 1936.

Dr. Pincoffs, as Editor of the ANNALS, said that he considered the object well within the purpose of the journal, and that the ANNALS should not be merely another clinical journal, but that it should express some purposes of the College. Either the Committee on Public Relations, or an expanded committee, might be appointed to select and prepare the series of articles proposed.

Dr. Miller pointed out that no cost is necessary. The College could adopt a working arrangement, putting the responsibility on the Committee for informing the American Medical Association of our willingness to coöperate with their program, asking their suggestions and working in harmony with what they have in mind. This would be merely a courteous gesture, the College offering to them this facility.

After some further discussion concerning the recommendations of Dr. Walsh, on motion by Dr. Miller, seconded by Dr. Pincoffs, and regularly carried, it was

Resolved, that the Committee be authorized to express the appreciation of the College to Dr. William Henry Walsh for his tendered coöperation and to express the feeling that the Board of Regents do not consider the time ripe for the adoption of a Council on Professional Service and Administrative Practice by the College.

On motion by Dr. Miller, seconded and regularly carried, it was

Resolved, that the College adopt the recommendation of the Committee on Public Relations, that the Editor of the ANNALS prepare an editorial concerning the discussion by the Board of Regents on the problem of medical economics and further arrange to publish in the ANNALS a series of articles of a purely educational and instructive nature on this problem. Furthermore, that the Committee inform the American Medical Association of our plan and ask for suggestions in an effort to harmonize our work with what they have in mind, this being a courteous gesture on the part of the College and an effort to offer to them this facility of our organization. Furthermore, the Committee on Public Relations, for this specific purpose, may be augmented by the addition of such members as are deemed helpful.

President Meakins thereupon appointed Dr. Maurice C. Pincoffs as an additional member, pro tem, of the Public Relations Committee, with authorization to the Chairman, Dr. James Alex. Miller, to add, pro tem, such additional members as he may see fit.

President Meakins called upon Dr. Alfred Stengel, General Chairman of the Philadelphia Clinical Session, to report upon local arrangements.

Dr. Stengel reported that he had delayed making local arrangements for clinics, giving the local profession time to rest up and get organized after the recent meeting in Philadelphia of the Interstate Postgraduate Medical Association. He has now organized his committees, selected several hospitals in which clinics will be given, and selected a chairman for each hospital. These chairmen have been requested to indicate the facilities they have available in the way of lecture rooms, exhibits, etc. In the next few weeks the program of clinics and demonstrations will be well underway. A new feature of the meeting in Philadelphia will be two morning meetings in lecture rooms at the auditorium in addition to the regular clinics. Guests, possibly a few local members, will be invited to give purely clinical talks for those who may elect them instead of hospital clinics. Seats will be reserved for Fellows of the College, and the balance of the space thrown open for guests from the County Medical Society, the Philadelphia College of Physicians and other local organizations.

On motion by Dr. White, seconded by Dr. Stroud, and regularly carried, it was

Resolved, that we discontinue inviting all the members of the local medical societies to register for attendance at the local clinics, due to overcrowding the members of the College for whom the program is arranged. It shall be provided, however, that the general sessions and, at the Philadelphia Session, the two lecture rooms in the auditorium be open for the free admission of all members of the County Medical Society and the members of the Philadelphia College of Physicians.

Dr. Jonathan C. Meakins, President of the College, reported upon the preparation for the general program of the Philadelphia Session. He reported that he proposes to have fewer papers, somewhat longer recesses in the middle of the afternoon meetings and to provide more freedom from scheduled meetings. He proposes to publish in the program the exact time for the appearance of each speaker, so that anyone who wants to hear a particular paper can tell definitely when the speaker will appear. Dr. Meakins further said that he had delayed making up the program of general sessions, so that all the material he accepts will be strictly up to date and the result of recent investigation.

The Executive Secretary reported that the physical arrangements have been taken care of, the Benjamin Franklin Hotel selected for hotel headquarters and the Municipal Auditorium for general headquarters and the meeting place for general sessions. The commercial exhibits will also be housed there. The exhibit charts were prepared some weeks ago, and more than two-thirds of the space has been contracted for by firms who will exhibit. He asked the feeling of the Board of Regents concerning the initiation of scientific exhibits, pointing out that such exhibits are fairly expensive and require much time and effort. No scientific exhibit should be initiated unless it will be of the highest quality. It seems that the conduct of the scientific exhibits should more or less be given to the American Medical Association, which has already conducted many such exhibits on a very high scale.

On motion by Dr. Piersol, seconded by Dr. White, and regularly carried, it was

Resolved, that the College shall not at the present time embark upon the plan of conducting scientific exhibits.

On motion by Dr. Meakins, seconded by Dr. Warren, and regularly carried, it was

Resolved, that the College of Physicians of Philadelphia be extended a vote of thanks from the Board of Regents of the American College of Physicians for their hospitality on the occasion of the Weir Mitchell Dinner on December 15, which our Board attended as a body.

The Board of Regents authorized the Committee on Credentials to hold a meeting on or before the end of March 1935, for the purpose of reviewing all proposals for membership to be acted upon during the Philadelphia Session.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

COLLEGE NEWS NOTES

Nominations for Elective Officers

The Committee on Nominations of The American College of Physicians, in accordance with the provisions of the By-Laws, presents the following nominations for the elective officers of the College for 1935–1936.

President-Elect, Ernest B. Bradley, M.D., Lexington, Ky.
First Vice-Pres., Arthur R. Elliott, M.D., Chicago, Ill.
Second Vice-Pres., David P. Barr, M.D., St. Louis, Mo.
Third Vice-Pres., James S. McLester, M.D., Birmingham, Ala.

Respectfully submitted,

Committee on Nominations,
Charles F. Martin, *Chairman*
Roger I. Lee
William J. Kerr
Charles H. Cocke
Gerald B. Webb

Gifts to the College Library

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Dr. Ralph Pemberton (Fellow), Philadelphia, Pa.—one book, "The Medical and Orthopaedic Management of Chronic Arthritis";

Dr. Henry P. Wright (Fellow), Montreal, Que.—one book, "Essentials of Infant Feeding and Paediatric Practice."

Acknowledgment is also made of the receipt of reprints from the following:

Dr. Ralph Oakley Clock (Fellow), New York—1 reprint;
Dr. Howard L. Hull (Fellow), Yakima, Wash.—1 reprint;
Dr. Paul H. Ringer (Fellow), Asheville, N. C.—4 reprints;
Dr. Albert H. Rowe (Fellow), Oakland, Calif.—8 reprints;
Dr. John C. Ruddock (Fellow), Los Angeles, Calif.—3 reprints;
Dr. Vincent J. Dardinski (Associate), Washington, D. C.—7 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint.

Major J. R. Darnall (Fellow) vacated, January 15, 1935, the office of Secretary-Treasurer of the Medical Association of the Isthmian Canal Zone, Panama, and was installed as Vice-President for 1935. Major James S. Simmons (Fellow), was installed as Secretary-Treasurer. The scientific program included an address by Major Darnall on the subject of "Diabetic Coma," and a presentation by Major J. G. Knauer (Associate), of electrocardiographic studies of "Some Interesting Cases of Coronary Thrombosis."

Dr. James L. McCartney (Fellow), formerly Director of the Northwest Retreat, Portland, Ore., has been appointed Director of the Institute for Mental Hygiene of the Battle Creek Sanitarium, Battle Creek, Mich. He will be in charge of the psychiatric work at the Sanitarium. The Sanitarium for some time has planned to establish a Department of Psychiatry, and with the appointment of Dr. McCartney, a modern psychiatric hospital of 75 beds is being opened to care for the constantly increasing demand for better facilities to treat nervous and mental cases.

The Thirty-First Annual Congress on Medical Education, Hospitals and Licensure was held at Chicago, February 18 to 19, 1935. Dr. James Alexander Miller

(Fellow), Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York, presented a paper on "Education of Physicians in Tuberculosis."

Dr. L. J. Moorman (Fellow), Dean, University of Oklahoma School of Medicine, Oklahoma City, presented a paper on "Some Historical Aspects of Tuberculosis."

Dr. J. A. Myers (Fellow), Professor of Medicine, Preventive Medicine and Public Health, University of Minnesota, Minneapolis, presented a paper on "Function of the General Hospital in the Treatment of Tuberculosis."

On the subject "Should the Radiologist, the Pathologist, and Anesthetist be Licensed to Practice Medicine?", Dr. B. R. Kirklin, Rochester, Minn., presented the case from the standpoint of the radiologist; Dr. James S. McLester (Fellow), Birmingham, Ala., from the standpoint of the internist; and Dr. Walter L. Bierring (Fellow), Des Moines, Ia., from the standpoint of the licensing board.

Dr. Harold Rypins (Fellow), Secretary, New York Board of Medical Examiners, Albany, presented a paper on "Are Interns Practicing Medicine?"

Dr. Daniel J. Glomset (Fellow), Des Moines, Ia., with Dr. Charles Gordon Heyd of New York, presented a paper on "Extension Teaching in Medicine."

Other Fellows of the College, who appeared on the program to discuss various papers, were:

Dr. Irving S. Cutter, Chicago
Dr. Willard C. Rappleye, New York
Dr. Henry C. Sweany, Chicago
Dr. James J. Waring, Denver
Dr. Kennon Dunham, Cincinnati
Dr. Edward S. McSweeney, New York
Dr. Albert Soiland, Los Angeles
Dr. J. J. Moore, Chicago

Dr. R. W. Bradshaw (Associate), College Physician to Oberlin College, Oberlin, Ohio, was reëlected President of the American Student Health Association at its last annual meeting in New York, December 27 to 28, 1934.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been appointed a member of the Editorial Board of the Review of Gastroenterology (New York), and is Vice-Chairman of the Abstract Staff.

OBITUARIES

JOHN ROWAN MORRISON

On the eighth of January, 1935, Dr. John Rowan Morrison, F.A.C.P., died after an illness of several months. He was born in the year 1877 in Oldhan County near Louisville, Kentucky, not only of pioneer Kentucky stock but of pioneer physicians stock as well. His father, Dr. A. M. Morrison, was an eminent Federal army surgeon in the war between the states, and two of his maternal uncles were physicians. He was a graduate of the old Louisville Medical College in 1898, and his postgraduate work was done in New York City at the Hospital for Ruptured and Crippled and later at Bellevue. After his internships Dr. Morrison returned to Louisville and despite the fact that he had been crippled since childhood by poliomyelitis he engaged in hard general practice for more than 20 years, later limiting his work to the field of internal medicine. Always progressive, he was one

of those responsible for the medical certification of milk, and for dairy herd testing in Kentucky. He assisted in the organization of Public Health Nursing in Louisville and in many other useful enterprises. Dr. Morrison was a valued teacher at the Louisville Medical School where he was a Clinical Professor of Medicine and his ward rounds have impressed upon many a medical student the value of original thinking and the avoidance of fads. An astute clinician, he arrived at a correct diagnosis quickly and accurately, and was much esteemed as a consultant.

Dr. Morrison was greatly loved for his kind encouragement to young physicians, cordially welcoming them into practice and helping them in many ways if he considered them worthy. He highly prized his Fellowship in the College of Physicians and was always interested in securing good men for the College in this community. Not only a skilled physician but a man of wide culture, a philosopher and a wit, his fellowship will be badly missed.

HARRY S. FRAZIER, M.D., F.A.C.P.,
Louisville, Ky.

E. RODNEY FISKE

Dr. E. Rodney Fiske, Fellow of the American College of Physicians since 1925, died December 19, 1934, of Hodgkin's disease. He was born in Brooklyn in 1873, received his preliminary education at the Brooklyn Polytechnic Institute, his B.A. degree from Columbia University, and his medical degree from the New York Homeopathic Medical College in 1895.

Dr. Fiske had served many hospitals and institutions during his career. At the time of his death he was associate professor of medicine at the New York Homeopathic Medical College and Hospital; associate attending physician to the Flower Hospital; consultant to the Yonkers (N. Y.) General Hospital, Brooklyn Nursery and Infants Hospital, and the Huntington (N. Y.) Hospital; and, chief of the department of medicine, Peck Memorial Hospital of Brooklyn.

He was a member of the Kings County Homeopathic Medical Society, New York State Homeopathic Medical Society, Academy of Medicine of New York, and the American Institute of Homeopathy. He was a member also of the Phi Beta Kappa honorary fraternity and a founder of the Alpha Sigma professional fraternity.

KENNETH G. MOWAT

Dr. Kenneth G. Mowat, Associate, of Buffalo, New York, died January 13, 1935, of a heart attack.

Dr. Mowat was born in 1885 and graduated from the University of Buffalo School of Medicine in 1924. He was an instructor in medicine in his Alma Mater. He was a member of the Erie County Medical Society, New York State Medical Association, Buffalo Academy of Medicine and the American Medical Association. He was elected an Associate of the American College of Physicians during 1928.